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DTU Environment
Department of Environmental Engineering

PhD Thesis
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Preface

The research presented in the present PhD thesis, entitled "Understanding and assessing potential environmental risks of nanomaterials: Emerging tools for emerging risks" was conducted at the Department of Environmental Engineering at the Technical University of Denmark under the supervision of Associate Professor Anders Baun. The PhD program ran from September 2007 through November 2010 and was funded by the Technical University of Denmark. The content of the PhD thesis is primarily based on five scientific journal articles as listed below. These articles formed the basis of the research within the PhD program. Both internal and external collaborators were involved in the successful completion of this work.

I. **Grieger K**, Hansen SF, Baun A. 2009. The known unknowns of nanomaterials: Describing and characterizing uncertainty within environmental, health and safety risks. Nanotoxicology 3(3): 1-12.

II. **Grieger K**, Baun A, Owen, R. 2010. Redefining risk research priorities for nanomaterials. Journal of Nanoparticle Research 2(2): 383–392.

III. **Grieger K**, Linkov I, Hansen SF, Baun A. 2010. Environmental risk analysis for nanomaterials: Review and evaluation of frameworks. Nanotoxicology– *Submitted*

IV. **Grieger K**, Fjordbøge A, Hartmann NB, Eriksson E, Bjerg PL, Baun A. 2010. Environmental benefits and risks of zero-valent iron nanoparticles (nZVI) for in situ remediation: Risk mitigation or trade-off? Journal of Contaminant Hydrology– *In Press*

V. **Grieger K**, Hansen SF, Sørensen PB, Baun A. 2010. Conceptual modeling for identification of worst case conditions in environmental risk assessment of nanomaterials using nZVI and C_{60} as case studies. Science of the Total Environment– *Submitted*

Papers **I-V** are not included in this web version but can be obtained from the library at
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In addition, the following journal articles, reports, book chapters, and other written work were also authored or co-authored during the PhD program. These also relate to the topic of this PhD thesis although not included herein.

Baun A, Hartmann NB, **Grieger K**, Kusk KO. 2008. Ecotoxicity of engineered nanoparticles to aquatic invertebrates – a brief review and recommendations for future toxicity testing. Ecotoxicology 17(5):387-395.

Baun A, Hartmann NB, **Grieger K**, Hansen SF. 2009. Setting the limits for engineered nanoparticles in European surface waters. Journal of Environmental Monitoring 11(10):1774 - 1781.

Elder A, Lynch I, **Grieger K**, Chan-Remillard S, Gatti A, Gnewuch H, Kenawy E, Korenstein R, Kuhlbusch T, Linker F, Matias S, Monteiro-Riviere N, Pinto VRS, Rudnitsky R, Savolainen K, Shvedova A. 2009. Human health risks of engineered nanomaterials: Critical knowledge gaps in nanomaterials risk assessment. In: Linkov, I. and Steevens, J. (eds.), Nanotechnology: Risks and benefits, Dordrecht: Springer, pp. 3-29.

Grieger K, Hansen SF, Baun A. 2009. Limitations of current risk assessment of nanomaterials and uncertainty analysis related to nanomaterials. In: Craye, M. (eds), Governance of nanotechnologies: Learning from past experiences with risks and innovative technologies, Report for FP 6 Co-ordination action: Risk-Bridge - Building Robust, Integrative Inter-Disciplinary Governance Models for Emerging and Existing Risks Riskfield 5 – Nanotechnologies, pp. 45-54.

Grieger K, Hansen SF, Baun A. 2010. Uncertainty analysis of environmental risks of nanoparticles. Encyclopedia of Environmental Management- *Submitted*

Hansen SF, **Grieger K**, Baun A. 2010. Regulation and risk assessment of nanomaterials. Encyclopedia of Environmental Management- *Submitted*

Hansen SF, **Grieger K**, Baun A. 2009. Limitations of current regulation of nanomaterials. In: Craye, M. (eds), Governance of nanotechnologies: Learning from past experiences with risks and innovative technologies, Report for FP 6 Co-ordination action: Risk-Bridge - Building Robust, Integrative Inter-Disciplinary Governance Models for Emerging and Existing Risks Riskfield 5 – Nanotechnologies, pp. 54-58.

Kristensen J, Vinding K, **Grieger K**, Hansen SF. 2009. Adopting eco-innovation in Danish polymer industry working with nanotechnology: drivers, barriers and future strategies. Nanotechnology Law & Business 6(416) (Fall 2009):416-440.

Owen R, Crane M, **Grieger K**, Handy R, Linkov I, Depledge M. 2009. Strategic approaches for the management of environmental risk uncertainties posed by nanomaterials. In: Linkov, I. and Steevens, J. (eds.), Nanotechnology: Risks and benefits, Dordrecht: Springer, pp. 369-384.

Sørensen P, Thomsen M, Assmuth T, **Grieger K**, Baun A. 2009. Conscious worst case definition for risk assessment, part I: A knowledge mapping approach for defining most critical risk factors in integrative risk management of chemicals and nanomaterials. Science of the Total Environment- *In press* (doi:10.1016/j.scitotenv.2009.11.010.)

Wickson F, **Grieger K**, Baun A. 2010. Nature and nanotechnology: Science, ideology and policy. International Journal of Emerging Technologies and Society 8(1):5-23.

Baun A, Hartmann NB, **Grieger K**, Hansen SF. 2009. Risikovurdering i nano-dimensioner: Øget anvendelse af nanomaterialer sætter nye krav til riskovurdering. Dansk Kemi 90(3):14-16.

Baun A, Hartmann NB, **Grieger K**, Hansen SF. 2010. Risikable nanomaterialer?- øget anvendelse af nanomaterialer sætter nye krav til risikovurdering. Aktuel Naturvidenskab 3:30-32.

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Summary

International research efforts are currently underway in order to understand and assess the potential environmental risks of engineered nanomaterials (NM). Thus far, these novel materials present significant challenges to scientists, researchers, governments, and policy-makers due to extensive knowledge gaps not only in understanding NM and their behaviour in complex environmental systems, but also in terms of suitable risk analysis tools and frameworks. In light of these challenges, this PhD thesis aims to: 1) describe the state of uncertainty within the potential environmental, health, and safety (EHS) risks of NM using a qualitative approach; 2) assess and evaluate various risk analysis frameworks for NM which have been proposed as alternatives to standard risk assessment; and 3) apply novel approaches for decision making regarding the potential environmental risks of selected NM. Ultimately, the information presented herein may help advance the fields of research which aim to better understand the potential environmental risks and uncertainties of NM and strategies to assess these.

Through the application of the Walker and Harremoës framework to describe and characterize uncertainty, it was found that there are extensive knowledge gaps in nearly all aspects of basic EHS knowledge of NM risks, although further research efforts are likely to reduce most uncertainties. It was also found that NM risk research has largely been directed at ultimately fulfilling the standard risk assessment framework despite that this process is likely to be very time- and resource-demanding. A number of risk analysis frameworks which may be alternative to standard risk assessment have been proposed for NM in recent years. Through a systematic evaluation of these alternative frameworks, it was found that most of these include a number of important criteria for successful risk analysis, including flexibility for multiple NM, suitability for multiple decision contexts, inclusion of life cycle perspectives and precautionary aspects, transparent, and handling of qualitative and quantitative data. However, most of them were mainly applicable to health (occupational) settings with minimal environmental risk considerations. It was also unclear if applications of the frameworks were "successful," due to the very limited number of applications on NM or NM-embedded products. In this way, it appears to be quite challenging to concurrently test 'new materials' with 'new tools.'

In a case study involving the use of zero-valent iron nanoparticles (nZVI) for *in situ* remediation, it was found that nZVI's potential to pose an environmental risk

is in between “best” and “worst” case conditions based on currently available data. This highlights that currently there do not appear to be significant grounds to form the basis that nZVI poses an extreme, apparent risk to the environment. However, the majority of the most serious criteria (persistency, bioaccumulation, toxicity) are largely unknown. In another application of novel approaches for decision-making which used the Worst-Case Definition model, the most probable worst-case conditions which are critical for inclusion in environmental risk assessments of nZVI were identified. These included nZVI accumulation in organism, production of reactive oxygen species, antioxidant balance disruption, cell membrane disruption, nZVI age and surface properties, acute exposure tolerance. Subsequent environmental risk assessments of nZVI should prioritize these parameters for maximum efficiency of assessments.

In light of these findings, it is first recommended that research in the field of nanoecotoxicology is prioritized towards the development of adequate assessment testing procedures and equipment, full characterization, and environmental fate and behavior of NM. This is due to the minimal presence of stochastic uncertainty in these areas as well as their frequency of citation as critical knowledge gaps. Research also within bioaccumulation and persistency should be prioritized, as these critical areas have been only scarcely studied thus far. Second, for the field of environmental risk assessment of NM it is recommended that a multi-faceted approach be used for a given NM risk context, in which different frameworks (or parts thereof) may be combined to maximize the overall utility for NM. This is due to the differing scopes and objectives of many of the proposed frameworks which may be alternative to standard risk assessment. In addition, these frameworks should be actively tested on a range of environmentally-relevant NM given the limited number of applications and minimal consideration of environmental parameters. Third, for research which aims to develop NM for sustainable applications including the use of nanoparticles for environmental remediation like nZVI, it is recommended that continued research efforts are directed towards engineering NM with potentially reduced (eco)toxicity and implementing monitoring at sites which actively use NM. In this way, risk prevention and management strategies may be implemented both up- and down-stream in NM innovation processes. Finally, in order to ensure the responsible development of NM it is critical that research platforms are dedicated to a continuous exchange of knowledge between NM-developers and those attempting to understand and assess their potential risks.

Dansk sammenfatning

Der er på nuværende tidspunkt sat gang i en hel del større internationale forskningsaktiviteter, der forsøger at skabe en forståelse og vurdering af de potentielle miljømæssige risici af menneskeskabte nanomaterialer (NM). Hidtil har disse nye materialer stillet væsentlige udfordringer til forskere, regeringer, interesseorganisationer og politiske beslutningstagere på grund af en udpræget mangel på viden. Her er ikke kun tale om manglende forståelse af NM og deres adfærd i komplekse miljøsystemer, men også om en mangel af egnede redskaber og rammer for risikovurdering. I lyset af disse udfordringer, er formålet med denne ph.d.-afhandling at: 1) beskrive tilstanden af usikkerhed i vurderingen af de potentielle miljø-, sundheds- og sikkerhedsmæssige risici af NM ved hjælp af en kvalitativ tilgang; 2) vurdere og evaluere forskellige alternative tilgangetil risikovurdering af NM; og 3) anvende nye metoder for beslutningstagning vedrørendede potentielle miljørisici af udvalgte NM. I sidste ende vil de oplysninger, der præsenteres i denne afhandling kunne medvirke til at fremme forskning, der sigter mod at forbedre forståelsen usikkerheder og mulige miljømæssige risici af NM, samt strategier til at vurdere disse.

Gennem anvendelsen af Walker og Harremoës metoden, der beskriver og karakteriserer usikkerhed, blev det konstateret, at der er en udpræget mangel på viden om næsten samtlige grundlæggende miljø- og sundhedsdimensioner af NM risici. Samtidig blev det blotlagt at de fleste usikkerheder formentligt kan reduceres gennem en fortsat forskningsindsats. Det blev også fundet, at forskning i risici af NM hovedsageligt har været rettet mod det traditionelle paradigme for risikovurdering, på trods af at denne tilgang forventes at være meget tids- og ressourcekrævende. Der er i de seneste år blevet foreslået en række alternative metoder for risikovurdering af NM, og ved en systematisk evaluering af disse , blev det fundet, at de fleste indeholder en række af de væsentligste kriterier for en vellykket risikovurdering. Herunder fleksibilitet for flere typer af NM, egnethed til flere beslutningssammenhænge, inddragelse af livscyklus- og forsigtighedsaspekter, gennemsigtighed, og håndtering af kvalitative og kvantitative data. De fleste var dog mest relevante i sundhedssammenhænge (arbejdsplads relateret), og kun i mindre grad for vurdering af miljømæssige risici. Det var også uklart, om anvendelsen af de forskellige alternative tilgange til risikovurdering kunne kaldes for en “succes”, da de kun i meget begrænset omfang er blevet anvendt på NM eller NM-baserede produkter. På denne måde har det vist sig at være ganske udfordrende at afprøve ”nye materialer” med ”nye værktøjer”.

I et casestudie om anvendelsen af nul-valente jernnanopartikler (nZVI) til in situ oprensning, blev det konstateret, at nZVIs potentiale for at udgøre en miljørisiko ligger mellem de ”bedste” og ”værste” mulige scenarier, vurderet på basis af de nuværende data. Derfor synes der ikke at være væsentlig grund til at vurdere, at nZVI udgør en ekstrem og tydelig risiko for miljøet. Dog er størstedelen af de mest alvorlige kriterier (persistens, bioakkumulering, toksicitet) stort set ukendte. I en anden anvendelse af nye tilgange til beslutningstagning er ”Worst-Case Definition” modellen blevet anvendt. Hervedblev de mest sandsynlige worst-case parametre for miljømæssige risikovurderinger af nZVI identificeret. Disse omfattede: ophobning af nZVI i organismer, produktionen af reaktive ilt arter, forstyrrelser af antioxidantbalance, cellemembransforstyrrelser, nZVI alders- og overfladesegenskaber, og akut eksponeringstolerance. Fremtidige miljømæssige risikovurderinger af nZVI bør prioritere disse parametre for at effektivisere deres evalueringer.

I lyset af disse resultater forslås en række forskningsindsatser. For det første anbefales det, at forskning i nanoøkotoksikologi prioriterer udviklingen af tilstrækkelige vurderingsprocedurer og -udstyr, omfattende karakterisering, samt NMs miljømæssige skæbne og opførsel. Dette skyldes en minimal tilstedeværelse af stokastisk usikkerhed på disse områder samt den hyppighed hvorved de bliver identificeret som kritiske for vidensopbygning. Forskning inden for bioakkumulering og persistens bør også prioriteres, da disse kritiske dimensioner indtil videre kun har været knapt undersøgt. For det andet, anbefales det, at der - i miljørisikovurdering og -analyse af NM - anvendes en mangesidet fremgangsmåde til evalueringen af givne NM risiko. Heri kan forskellige rammer (eller dele deraf) kombineres til at maksimere den overordnede nytte eller styrke af NM-vurderingerFor det tredje anbefales det, for forskning der sigter mod at udvikle NM for bæredygtige anvendelser, herunder anvendelsen af nanopartikler såsom nZVI til udbedring af miljøskader, at en fortsat forskningsindsats rettes mod udviklingen af NM med potentielt nedsat (øko)toksicitet samt etableringen af kontrol, hvor NM anvendes aktivt. På denne måde kan strategier til forebyggelse og styring af risici gennemføres både opstrøms og nedstrøms i NM innovationsprocesser. Endelig er det, for at sikre en ansvarlig udvikling af NM, afgørende, at forskningsplatforme eller -paneler bliver dedikeret til en løbende udveksling af viden og ideer mellem NM-udviklere og dem, der forsøger at forstå og vurdere deres potentielle risici.

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1 Introduction

Assessing the potential environmental risks of nanomaterials (NM) is an extremely complex and multi-disciplinary field. Not only is knowledge needed within understanding NM themselves and their behavior in abiotic and biotic systems, but adequate risk assessment tools and frameworks are also needed in order to aid subsequent decisions regarding these risks. In addition to many other aspects, this information and data in these fields are currently unavailable due to severe knowledge gaps associated with these novel materials. At the same time, the variety and number of NM and their embedded applications further hamper risk assessments. In response to these challenges, scientists, researchers, governments, international organizations, and other stakeholders are currently in pursuit of not only the knowledge regarding the potential environmental risks of NM but also in terms of the adequate tools, frameworks, and approaches needed to assess these risks. These areas remain current topics for debate and are explored in more depth in the present PhD thesis.

First, the following chapter provides a brief overview of the emergence of nanotechnology and engineered NM and growing concerns regarding their potential environmental risks. This is intended to place the emergence of these novel materials and applications in a broader scope. The objectives of the PhD thesis are also presented at the end of this chapter. Then, more detailed information on aspects related to the potential environmental risks of NM and strategies to assess them will be presented in the subsequent chapters of the thesis (Chapters 2-4). Finally, overall conclusions from the PhD study as well as further perspectives are presented (Chapter 5).

Herein, a "nanomaterial" is defined as a "material having one or more external dimensions in the nanoscale or which is nanostructured" as defined by the British Standards Institution (2007) and which includes nanoparticles, nanostructured surfaces or bulk forms as defined by the International Organization for Standardization (ISO 2008). For reference purposes, the prefix "nano" indicates one in a billion and therefore a nanometer (nm) is 10^{-9} meters. Currently, the exact definition of "nanomaterial" is still subject to debate (e.g. ISO 2010; Lövestam et al. 2010; SCENIHR 2010), although it is generally considered to be a material in which there is at least one dimension between 1 and 100 nm and have different functionalities compared to their bulk-scale counterparts. In addition, this thesis focuses primarily on the potential environmental risks of

NM, although there is also some overlap to related aspects of human health due to the particularly sparse amount of data which solely relates to the environment (Baun et al. 2009) and the inevitable connection between the environment and human health.

1.1 Development of nanomaterials

In December 1959, the Nobel Laureate Richard Feynman gave an infamous lecture entitled “There’s plenty of room at the bottom” at the California Institute of Technology during a meeting with the American Physical Society (Feynman 1960). At this meeting he first mentioned the process which could potentially manipulate individual atoms and molecules and hence advance the field of synthetic chemistry. This type of technology would later be officially termed “nanotechnology” in 1974 in order to describe the process of moving or manipulating atoms at the nano-scale (1-100 nm) (Taniguchi 1974). Subsequent advances in the field of nanotechnology were made including the development of engineered NM in the 1980’s and 1990’s. Among these were for instance some of the first carbon-based NM, including C_{60} fullerene nanoparticles (“buckyballs”) in 1985 and carbon nanotubes (CNT) in 1991 (Wolf 2004). Hence, the field of nanotechnology including the development of engineered NM was born with anticipated applications in fields of for instance physics and electronics along with e.g. medicine and consumer applications (Adlakha-Hutcheon et al. 2009). Today, advancements in these fields are progressing rapidly as scientific research and funding has been rapidly growing on an international scale (Holman 2007), with an estimated market value for nanotechnology-related applications expected to reach between $1 trillion and $2.9 trillion in the next five years (Holman 2007; Stone et al. 2010).

One area in which NM are readily being used and incorporated in at increasing rates are consumer products. In 2006 there were an estimated 212 “manufacturer-identified nanotechnology-based” consumer products on the market (Hansen et al. 2008a). Today in 2010 there are currently over 1,000 products (Woodrow Wilson Center 2010). These products range from applications within e.g. automotive equipment and accessories to electronics as well as food packaging materials. In addition, the field of nanomedicine including e.g. drug delivery devices to advance cancer treatments is also one of the most rapidly advancing areas within nanotechnology development with many anticipated societal benefits (Holman 2007; Adlakha-Hutcheon et al. 2009; Linkov and Steevens

2009). At the same time, many NM are also being used in environmentally-beneficial products or applications, also termed “green” nano-technologies and materials, including the use of NM to purify water (e.g. “life straw,” Vestergaard 2010) and remediate the environment (e.g. zero-valent iron nanoparticles, Chang and Kang 2009), detect contaminants (Riu et al. 2006), as well as improve energy efficiency and renewable energy applications (e.g. solar cells, Bullis 2006). In essence, nanotechnology and the use of NM have the potential to become widespread in society, even plausibly ubiquitous in nature, with many potential environmentally- and socially-beneficial applications (RCEP 2008).

1.2 Potential environmental risks

Along with the advancements of NM development and use, there has also been the development of growing concerns over their potential environmental, health, and safety (EHS) risks (e.g. The Royal Society and The Royal Academy of Engineering 2004; Maynard 2006b; SCENIHR 2007; US EPA 2007; FOE 2008; Stone et al. 2010). This has been primarily due to their nano-scale dimensions which tend to be highly reactive, mainly due to high surface-to-mass ratios, and may behave differently than their bulk scale counterparts (RCEP 2008). For example, compared to bulk materials NM may exhibit different e.g. solubility, electrical conductivity, material strength, and magnetic behavior (Oberdörster et al. 2005). In fact for the most part NM are indeed considered to be ‘novel’ materials, many of which were developed to take advantage of their highly reactive properties. Concern over a greater degree of reactivity is due to the fact that enhanced chemical reactivity may lead to an increased production of e.g. reactive oxygen species (ROS) which has been associated with oxidative stress, inflammation, and damage to DNA and proteins (Nel et al. 2006). All of these concerns are relevant for both environmental and human health.

Moreover, many NM may have additional surface coatings or functionalizations which ultimately have the possibility to create a plethora of diverse NM. For example, it has been estimated that 50,000 different types of single walled CNT may be produced (although not all commercially relevant) from different manufacturing and purification methods as well as the application of a surface coatings (Schmidt 2007). Each of these different types may in fact have different physicochemical or biological properties, and exemplifies the complexity and variety of NM in their different forms. In addition, growing concerns regarding their potential environmental and health risks have also related to their potential for widespread exposures given the variety of applications and products in which they are found (RCEP 2008; SCENIHR 2009; Wijnhoven et al. 2009). While there have been some preliminary estimates at the concentrations and types of NM likely to be released to environment (Mueller and Nowack 2008; Gottschalk et al. 2010) along with some applicable studies to occupational settings from the field of air pollution (Stone et al. 2010), there are still major challenges to measure or quantify them particularly due to e.g. the lack of proper equipment and procedures for these analyses (Hassellov et al. 2008; NIOSH 2009).

Mounting concerns regarding the potential environmental risks of NM have also been in light of previous experiences with some harmful chemicals or substances, in which knowledge of their potential to cause adverse effects and the extent of exposures were unknown before their widespread use (e.g. polychlorinated biphenyls, chlorofluorocarbons) (EEA 2001). In addition, growing concerns have also been in light of the potential for long-term and wide-spread effects from exposure to NM (e.g. potential for persistency, low environmental degradability, and use in a wide range of applications), as well as high economic stakes under extensive scientific uncertainty, similar to other large-scale environmental challenges such as climate change and genetically modified crops (Krayer von Krauss et al. 2008; van der Sluijs et al. 2008; Gee 2009). Given these past experiences, a variety of stakeholders are currently interested in better understanding and assessing the potential environment (and health) risks of NM, both in terms of preventing adverse effects but also to ensure the responsible development of NM and nano-products (Maynard 2006a; Owen et al. 2009). One of the main challenges, however, is overcoming the numerous and extensive uncertainties in these assessments not only in terms of, for instance, exposure and effects but also in terms of developing standardized testing methods and equipment as well as better understanding the behavior of NM themselves (SCENIHR 2009). These challenges are further amplified not only by the diversity of NM, the role of applied coatings or functionalizations, products and applications in which they are contained, but also by the rate of NM and nano-product innovation (Linkov et al. 2009a). All of these challenges presently exist for the 1st and potentially 2nd 'generations' of NM, let alone for the subsequent 3rd and 4th generations that are expected to emerge in coming years and decades (Roco and Renn 2006), which may only amplify current limitations to assessing the potential risks of NM given their increased complexity. In response to some of these obstacles in understanding the potential environmental risks of NM, some government agencies and organizations have responded recently by recommending or requesting different regulatory or labeling obligations, such as the use of NM in cosmetics (European Commission 2009), food and feed (Duprez and Nazer 2010), and electronic products (Houlton 2010).

To date, research that attempts to assess the potential environmental and health risks of NM has been challenging given these aforementioned uncertainties and difficulties with dealing with new materials (OECD 2009a, b; SCENIHR 2009). Among numerous other research questions, scientists, governments, regulatory bodies, and international organizations have been asking:

- What are the “knowns” and “unknowns” regarding the potential EHS risks of NM?
- How should research be prioritized in order to most effectively reduce knowledge gaps?
- Are standard or traditional risk assessment tools and frameworks applicable to NM, or are new assessment methods and/or frameworks needed?
- What are some alternative approaches to assessing these risks which have been proposed, and are they applicable to NM?

These issues are among some of the main challenges to understanding, assessing, and managing the potential environmental risks of NM, and which are currently the topic of intense international debate and the subject of on-going research e.g. (Aguar and Murcia 2008; SCENIHR 2009; OECD 2010).

1.3 Thesis scope and objectives

This PhD thesis focuses primarily on the potential environmental risks of NM and approaches to assess these risks. Due to the complex nature of understanding and evaluating the potential environmental risks of novel NM as well as analyzing assessment strategies, the present PhD thesis and research presented within involves the interaction of a number of major scientific disciplines and fields, such as environmental risk assessment, scientific uncertainty, and decision making. This may be similar to assessing the potential environmental risks of other complex environmental challenges. Within this thesis, state-of-the-art knowledge as well as synopses from original research carried out during the PhD program will be presented.

More specifically this PhD thesis has the following objectives, which are then supported by the results of several scientific journal articles included in the Appendix:

1. Describe and characterize scientific uncertainty within environmental, health, and safety risks of nanomaterials, based upon the application of the Walker and Harremoës framework (Paper I);

2. Assess and evaluate alternative frameworks for addressing the environmental risks of nanomaterials based on select criteria (Papers II, III);

3. Apply novel approaches or strategies for decision making regarding the potential environmental risks of nanoparticles used for environmentally-beneficial applications based on case studies (Papers IV, V)

2 Uncertainty within environmental, health, and safety risks of nanomaterials

In the pursuit of science and innovation, uncertainty in regards to the potential environmental, health, and safety (EHS) risks of novel discoveries and new materials is an inherent factor (Renn 2008; The National Academies of Science 2008). This is also particularly relevant and applicable to the development of NM and NM-embedded applications, in which NM may have different or additional functionalities compared to bulk materials and there are many fundamental uncertainties regarding the potential environmental and health risks of NM (e.g. RCEP 2008). With growing concern regarding these potential risks, many scientists, international organizations, governmental bodies, and other institutions have responded by identifying various knowledge gaps or research needs in the field (e.g. DEFRA 2007; Owen and Handy 2007; SCENIHR 2007, 2009; Baun et al. 2008; ICON 2008; NNI 2008; Alvarez et al. 2009; Morris et al. 2009; Seaton et al. 2009; Wiesner et al. 2009; Stone et al. 2010). Presently, scientific research which aims to reduce these areas of uncertainty within better understanding the potential environmental and health risks of NM is actively underway at national and international scales (e.g. Aguar and Murcia 2008; ISO 2010; OECD 2010).

However as seen with the introduction of synthetic chemicals, many years or decades in fact were needed in many cases in order to fully understand their potential environmental and/or health consequences (EEA 2001; Abt et al. 2010). In the case of NM, some have estimated that decades may also be needed in order to acquire the adequate research knowledge in order to complete risk assessments (Maynard 2006a; RCEP 2008; Choi et al. 2009). Therefore, the presence of scientific uncertainty within understanding the potential EHS risks of NM is not likely to be eliminated in the near future and hence, strategies to understand and assess these uncertainties may be one first step to better understand the extent and nature of the knowledge gaps (and also the risk itself) as well as formulate strategies to handle them (Stern and Fineberg 1996; Walker et al. 2003). This chapter aims to explore these concepts of better understanding the scientific uncertainty within the EHS risks of NM and as well as demonstrate the application of a framework to describe and characterize uncertainty in this field.

2.1 Importance of scientific uncertainty

The important role that uncertainty plays in assessments of risks to the environment or health has been increasingly recognized by a variety of scientists, government agencies, and other institutions (Funtowicz and Ravetz 1990; EEA 2001; Krayer von Krauss et al. 2005; WHO 2006; The National Academies of Science 2008; RCEP 2008; van der Sluijs et al. 2008; Gee 2009; Abt et al. 2010). For complex environmental and public heath issues which are also often policy-relevant including the case of nanotechnology and NM, the role of uncertainty may be even larger than in traditional scientific endeavors (van der Sluijs et al. 2008). This is due to the fact that these cases are often on global scales, may potentially have long-term effects, involve extensive uncertainties in terms of their potential risks, often have regulatory implications, and have deep social and ethical aspects (Funtowicz and Ravetz 1990; Abt et al. 2010). Some have termed these scientific risk issues which reach beyond the standard bounds of what is normally considered to be traditional science as 'trans-scientific problems' (Weinberg 1972).

Due to the extensive uncertainties as well as the often high economic and health or environmental stakes, the role of uncertainty in these trans-scientific problems is an essential factor to consider in order to not only better understand the potential scientific risks but also to help improve decision making in these regards (The National Academies of Science 2008; Abt et al. 2010). Other proposed advantages of sufficiently describing and characterizing scientific uncertainties within complex issues include:

- improved comprehension of the different types of uncertainties;
- better informed strategies to cope with the identified uncertainties;
- better directed research strategies and funds by identifying those uncertainties which may or may not be reduced by additional research efforts;
- improved communication to a wide range of stakeholders regarding the nature and complexity of the risk in question;
- better informed adaptive decision-making strategies;
- increased transparency and openness with the risk characterization process (Stern and Fineberg 1996; Krayer von Krauss et al. 2005, 2006).

In addition, recommendations made by the European Environment Agency after a review of past experiences dealing with chemicals and other substances included "manage 'uncertainty' and 'ignorance' as well as 'risk'" and "identify and reduce 'blind spots' in the sciences used" (EEA 2001). Furthermore, other scientific organizations such as the Intergovernmental Panel on Climate Change have also identified the need for more descriptive information on scientific uncertainty by including additional information such as probability (e.g. 66-99%, 90-99%) as well as qualitative descriptors (e.g. 'likely,' 'very likely', 'beyond all reasonable doubt') (IPCC 2011). Therefore, an adequate identification and characterization of uncertainty within complex scientific issues has been suggested by several scientists and organizations as a part of strategies to respond more robustly to these issues.

More comprehensive and qualitative approaches to address various types of uncertainties within complex environmental and public health (i.e. trans-science) issues are mainly in response to traditional or more standard approaches to consider, and in many cases quantify, uncertainty as one of the predominant methods to further understand or handle uncertainty. Traditional means of handling uncertainty has been through the use of assumptions, extrapolations, or safety factors to attempt to compensate for a lack of data (Kandlikar et al. 2007). These are also often in conjunction with or included within environmental and health risk assessments. For example, among other approaches, Monte Carlo analysis, sensitivity analysis, data uncertainty engine, and inverse modeling (parameter estimation or predictive uncertainty) are all established quantitative tools which attempt to analyze scientific uncertainty often separately or subsequent to modeling analyses (Refsgaard et al. 2007). Monte Carlo uncertainty analysis (Poulter 1998) and sensitivity analysis (Pilkey and Pilkey 2007) are in fact among some of the most frequently proposed tools to analyze uncertainty in environmental risk challenges.

These aforementioned standard approaches and methods have been cited to be particularly useful under well-understood or controlled conditions or highly repetitive events (Funtowicz and Ravetz 1990; INTARESE 2006). However, their use in many environmental and health issues which are highly complex in nature has also been criticized (Funtowicz and Ravetz 1990; Ravetz 2005; Dale et al. 2008). For instance, these standard approaches may, among other limitations, over-simply the system(s) involved and reduce the 'true' state of uncertainty to over-simplified uncertainty parameters or factors (INTARESE 2006). These authors also cite a lack of recognition of different types of uncertainties as well as a misclassification of some fundamental types of uncertainties as ‘statistical,’ which may be then treated with e.g. uncertainty factors (INTARESE 2006). Furthermore, large amounts of data which are often needed to complete detailed quantitative uncertainty analyses in risk assessment frameworks are frequently unavailable, especially in the case of complex health and environmental risk issues (Abt et al. 2010). In response to these limitations of traditional approaches to assessing or handling uncertainty, a number of alternative tools and methods have also been proposed, including among others NUSAP (Numerical, Unit, Spread, Assessment and Pedigree) (Janssen et al. 2003; van der Sluijs et al. 2005), expert elicitation (Morgan 2005), stakeholder involvement (Gavelin et al. 2007), scenario analysis (Van Der Heijden 1996), as well as the uncertainty matrix (Walker et al. 2003). For a more complete overview and comparison of the different tools and methods available to deal with uncertainty in environmental modelling refer to (Refsgaard et al. 2007).

2.2 Uncertainty and nanomaterials

In the case of NM, the presence of uncertainty within understanding the potential risks to the environment or human health is important to consider for a number of reasons. First, uncertainty may be one of the main parameters which have the potential to limit the development of nanotechnology and NM (The Royal Society and The Royal Academy of Engineering 2004; Maynard 2006b; Bozeman et al. 2008). As there are a number of NM and NM-embedded applications which may be beneficial to the environment, including e.g. renewal energy applications, environmental remediation, or society such as e.g. nanomedicines, including the potential for great economic growth, the presence of uncertainty may ultimately result in unrealized benefits. Second, a more comprehensive recognition of the types of uncertainties involved in discussions of NM risks may also help ensure the responsible development of NM and NM applications. For instance, descriptive information on the uncertainties involved may aid NM risk characterization processes and/or help choose ‘safer’ alternatives by selecting options (or NM) with for instance less inherent uncertainty (Stebbing 2009). Third, more descriptive information on the uncertainties may also aid in more accurate communication and descriptions of the potential risks involved with NM. This is especially important given the rapidly growing number of NM and nano-products on the market (Hansen et al.

2008a; Woodrow Wilson Center 2010). In essence, there is a need to consider the uncertainties involved within the potential EHS risks of NM while attempting to reap the potential benefits of NM and nanotechnology applications and minimizing potential environmental or health (or economic) risks.

To date, the predominant method to address the various uncertainties pertaining to the potential EHS risks of NM has mainly been the description or listing of various knowledge gaps in the field. This has resulted in a number of different scientific journal articles or reports highlighting the current state of knowledge ("known-knowns") within the EHS risks of NM as well as the areas of uncertainty ("known-unknowns") (SCENIHR 2007, 2009; Owen and Handy 2007; NNI 2008; Aitken et al. 2009; Alvarez et al. 2009; Stone et al. 2010). For example, among other lists of "known-unknowns" the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded in their 2007 report:

> "…key mechanisms for exposure processes and toxicity effects of manufactured nanomaterials are not sufficiently understood…These uncertainties include the following: 1. the persistence of nanoparticles in the atmosphere, which will depend on rates of agglomeration and deagglomeration, and on degradation; 2. the relevance of routes of exposure to individual circumstances; 3. the metrics used for exposure measurements; 4. the mechanisms of translocation to different parts of the body and the possibility of degradation after nanoparticles enter the body; 5. the mechanisms of toxicity of nanoparticles; 6. the phenomenon of transfer between various environmental media. It should be emphasised that these are not simply uncertainties in the values of some traditional parameters, but rather the uncertainties about the potentially unique or significantly modified causal mechanisms themselves."

Although there have been some advancements in these fields since 2007 (e.g. Blaser et al. 2008; Kaegi et al. 2008; Auffan et al. 2009a, 2009b; Bhabra et al. 2009; Gottschalk et al. 2009, 2010; Nel et al. 2009; Geranio et al. 2009; Johnston et al. 2010), there are still extensive knowledge gaps in these areas (SCENIHR 2009) and it is still too early to form generalizations or trends for many NM or NM groups (Stone et al. 2010). Moreover, there have also been questions regarding the utility of many of the early (eco)toxicology studies, due to e.g. the use of unrealistic exposure doses and e.g. the influence of dispersants (Oberdörster 2010). In addition, there have also been a number of critical research gaps within developing proper NM testing methodologies and equipment (OECD 2009b), including knowledge regarding the best metrics to use in testing (e.g. Auffan et al. 2009b) and even the exact definition of NM and nanoparticles (ISO 2008, 2010; Lövestam et al. 2010; SCENIHR 2010). Some have even cited the disproportional number of studies which concentrate on hazard-related aspects compared to those focusing on exposure (Aitken et al. 2009; Maynard 2010). As a response to many of these challenges, research is currently underway in order to evaluate the appropriateness of methodologies used to assess the environmental and health risks of NM along with the development of equipment and tools (European Commission 2008; OECD 2009a, 2009b; ISO 2010).

These identifications of knowledge gaps have been extremely important to highlight the uncertainties as well as focus both short-term and long-term research needs. However, additional analyses including more descriptive information regarding the uncertainties themselves may be needed to more fully characterize the uncertainty and more accurately communicate the associated risks of NM. In addition, only a few other attempts to date have been made to specifically assess or handle the scientific uncertainty within the potential EHS risks of NM, most of which have been in conjunction with efforts that involve NM risk analyses or estimates. For instance, Monte Carlo uncertainty and sensitivity analyses have been used in a recent environmental modeling study which aimed to estimate predicted environmental concentrations of three nanoparticles in Switzerland (Gottschalk et al. 2010). In this study the authors handled the extensive uncertainties through the use of probability distributions for all parameters within the probabilistic material flow analysis. To date, this has been the only study which has provided a framework to use quantitative methods to include uncertainty in parameters pertaining to the environmental or health risks of NM to this author's knowledge. However given extensive data gaps used in the modeling, the results of this study may be subject to deeper, more fundamental types of uncertainty which lay beyond statistical bounds.

In addition, expert elicitation has been used by Morgan (Morgan 2005) to help fill data gaps pertaining to the health and environmental risks of NM. Kandlikar et al. (2007) also used expert elicitation to demonstrate the degree of consensus or disagreement among scientists involved in EHS risks of NM. In fact, the use of expert elicitation or similar measures has also been used in other attempts to provide preliminary NM risk characterization information, including identification of uncertainty within the life-cycle of some NM or nano-products (Davis 2007; Davis et al. 2008; Shatkin 2008; US EPA 2010a), within processes used to rank the relative risks of some NM (using Multi-Criteria Decision Analysis (Tervonen et al. 2009)), and the application of Bayesian Networks in NM risk characterization processes (Money 2010). In these applications, the use of expert elicitation has mainly involved the process of gathering various experts and using their knowledge to help identify the areas of uncertainty or to outline specific knowledge within a field, similar to its application in other environmental risk challenges (Krayer von Krauss et al. 2005).

2.3 Application of the Walker and Harremoës framework

Apart from the previously mentioned attempts which aimed to assess, describe, or handle uncertainty within the potential EHS risks of NM, Grieger et al. (2009 - Paper I in Appendix) published the only peer-reviewed analysis to date which focuses primarily on characterizing and describing this scientific uncertainty using a qualitative-based framework. Given the early stage of knowledge regarding NM in general and their potential impacts on the environment and health, a qualitative approach was used to characterize and describe uncertainty in these fields – an approach also recommended by the National Research Council (2009) in cases of extensive data gaps (Abt et al. 2010). The analysis by Grieger et al. (2009) was based on a review of published scientific literature from scientists, international bodies, government agencies, and organizations in order to systematically identify and characterize uncertainty within the EHS risks of NM using the Walker and Harremoës framework (Walker et al. 2003). This analysis aimed to not only identify and characterize the main areas of uncertainty in these regards but also to characterize the uncertainty in terms of its level (ranging from deterministic knowledge to ignorance) as well as its nature (reducible or stochastic). These descriptive factors of uncertainty were termed as "location," "level," and "nature," respectively, by Walker et al. (2003) and subsequently used by Grieger et al. (2009).

2.3.1 Methodology

Thirty-one published and peer-reviewed reports and review articles from leading scientists, government bodies, and international and national organizations on issues of the potential EHS risks of NM were screened as the basis for the analysis (Table 1). While all of the selected reports and articles focused on the potential EHS risks of NM, they were not original primary research articles (i.e. original results from e.g. specific testing of various nanoparticles). Social, ethical, or economic risks were also excluded from this analysis.

The selected literature was screened for acknowledged scientific uncertainty or a lack of knowledge pertaining to potential EHS risks of NM, including all forms of NM (e.g. nanoparticles, nano-structured surfaces, ISO 2008), as recognized by the authors of the literature. The different types of uncertainty termed "sub-locations" were recorded in their frequency of acknowledgement in the screened literature (i.e. how often they were mentioned in the report or article) along with the page number(s) on which they were found (for referral, if necessary). The sub-locations were then grouped into larger categories ("locations") in order to evaluate trends or patterns.

Table 1. Selected literature used by Grieger et al. (2009- Paper I) which were screened for recognized scientific uncertainty and/or lack of knowledge pertaining to potential EHS risks of NM

Reports	
• Breggin and Pendergrass 2007	• The Royal Society and The Royal Academy of Engineering 2004
• Council for Science and Technology 2007	• The Royal Society and The Royal Academy of Engineering 2006
• DEFRA 2006	• UNEP 2007
• DEFRA 2007	• US EPA 2007
• Environmental Defense and Dupont 2007a	• US FDA 2007
• European Commission 2004	
• Goldman and Coussens 2005	**Review articles**
• Lindberg and Quinn 2007	• Balbus et al. 2007
• Maynard 2006a	• Helland et al. 2007
• Maynard 2006b	• Holsapple et al. 2005
• Maynard et al. 2006	• Nowack and Bucheli 2007
• National Nanotechnology Strategy Taskforce 2006	• Oberdörster et al. 2005
• NIOSH 2006	• Rickerby and Morris 2007
• NNI 2006	• Singh and Nalwam 2007
• OECD 2007	• Stern and McNeil 2008
• SCENIHR 2006	• Wiesner et al. 2006
• SCENIHR 2007	

The total frequency of citation of each sub-location and location as found in the screened literature were then compared to the total number of citations of uncertainty in order to estimate the "level" of uncertainty for each location. This was done through the application of a 3-point system, in which a '1' represented low uncertainty, '2' medium uncertainty, and '3' high uncertainty, similar to other studies (Janssen et al. 2003; Refsgaard et al. 2007). Following this approach, a value of '1' (low uncertainty) was given to locations which comprised >25% of the total uncertainty citations, a '2' (medium) to locations comprising 15-25%, and '3' (high) for locations with <15% of total citations. This scoring was based on the presumption that an inverse relationship exists between how often a location was cited as an area of uncertainty and the overall level of scientific uncertainty, given that research has shown that it is nearly impossible to pose relevant questions when there is ignorance or a lack of relevant knowledge (Bloom et al. 1956; Dori and Herscovitz 1999; Fotta 2003; LaDuke 2004). The level of uncertainty for each location was also classified as either statistical (known outcomes and probabilities), scenario (known outcomes, unknown probabilities), or recognized ignorance (unknown outcomes, unknown probabilities) in an attempt to reflect the overall level of uncertainty in the screened literature.

The "nature" of uncertainty was estimated as either epistemic or stochastic by qualitatively assigning this for each location by the authors of the analysis. This was done in a manner that also attempted to reflect the nature of uncertainty of each identified location as indicated in the screened literature. Uncertainty that is epistemic in its nature may be potentially reduced through additional research efforts (e.g. larger sample sizes) as opposed to stochastic uncertainty which is inherent in the system and thus irreducible (e.g. annual rainfall events at a particular location) (Walker et al. 2003).

2.3.2 Results and discussion

Location: A total of 2,752 different citations of uncertainty were found in relation to the potential EHS risks of NM after screening the selected literature (Figure 1). These were distributed over four main locations of uncertainty (Figure 2): i) testing considerations (comprising 31% of total uncertainty citations found) which included how to perform various tests on NM (e.g. equipment, methodology, risk assessment procedures); ii) effect assessments (25%) which included general fields of toxicology and ecotoxicology in addition to specific adverse effects (e.g. genotoxicity, neurotoxicity) or phenomenon (e.g. translocation in organism, bioaccumulation); iii) characterization of NM (21%)

which included inherent properties of NM and e.g. how they behave in organisms or the environment; and iv) exposure assessments (13%) which included parameters relevant for human and environmental exposures routes (e.g. tools that limit exposure, uptake routes). There were also other locations which were found although less frequently (each comprising <5%), such as those pertaining to exact definitions of NM (termed defining NM), commercial-related uncertainties (commercial) including life cycle assessments, and unspecific uncertainties (unspecific), which were very general and without specific reference. Refer to Paper I in the Appendix for a complete list and description of all locations and sub-locations of uncertainty as identified in this analysis.

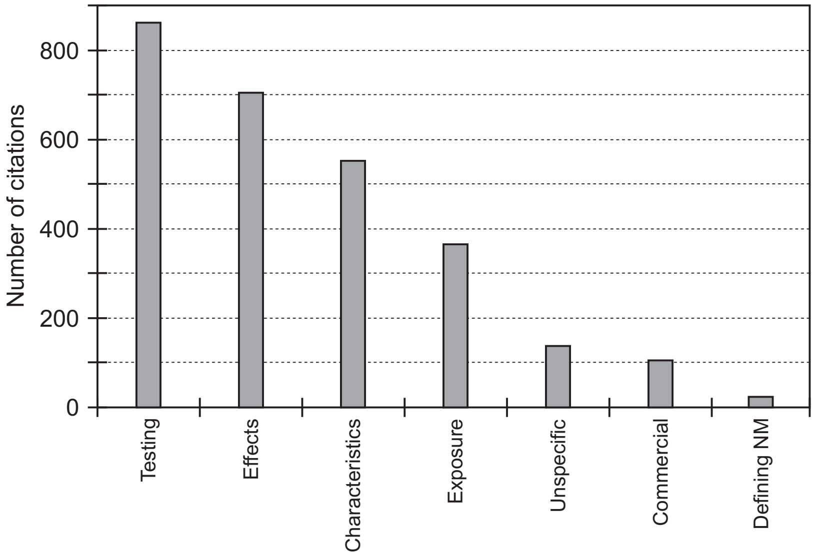


Figure 1. Total number of citations for identified locations of uncertainty pertaining to the potential EHS risks of NM (Grieger et al. 2009- Paper I).

In total, there were 56 separate sub-locations of uncertainty distributed across all locations (Figure 3). As mentioned in preceding sections, these sub-locations were then grouped into larger categories to form the previously-described locations. Across all sub-locations (Figure 3), the five most frequently cited included: i) uncertainty within the general effects assessment (i.e. lack of knowledge within the general phenomenon of human or environmental effects from NM without referring to any specific parameter) with 220 different citations found (e.g. "Toxicity … of engineered nanomaterials is largely unknown," Goldman and Coussens 2005); ii) lack of reference materials and standardization within testing considerations with 194 citations (e.g. "It should also be noted that reference materials for the evaluation of nanoparticles have not yet been identified," SCENIHR 2007); iii) characterizing the environmental fate and

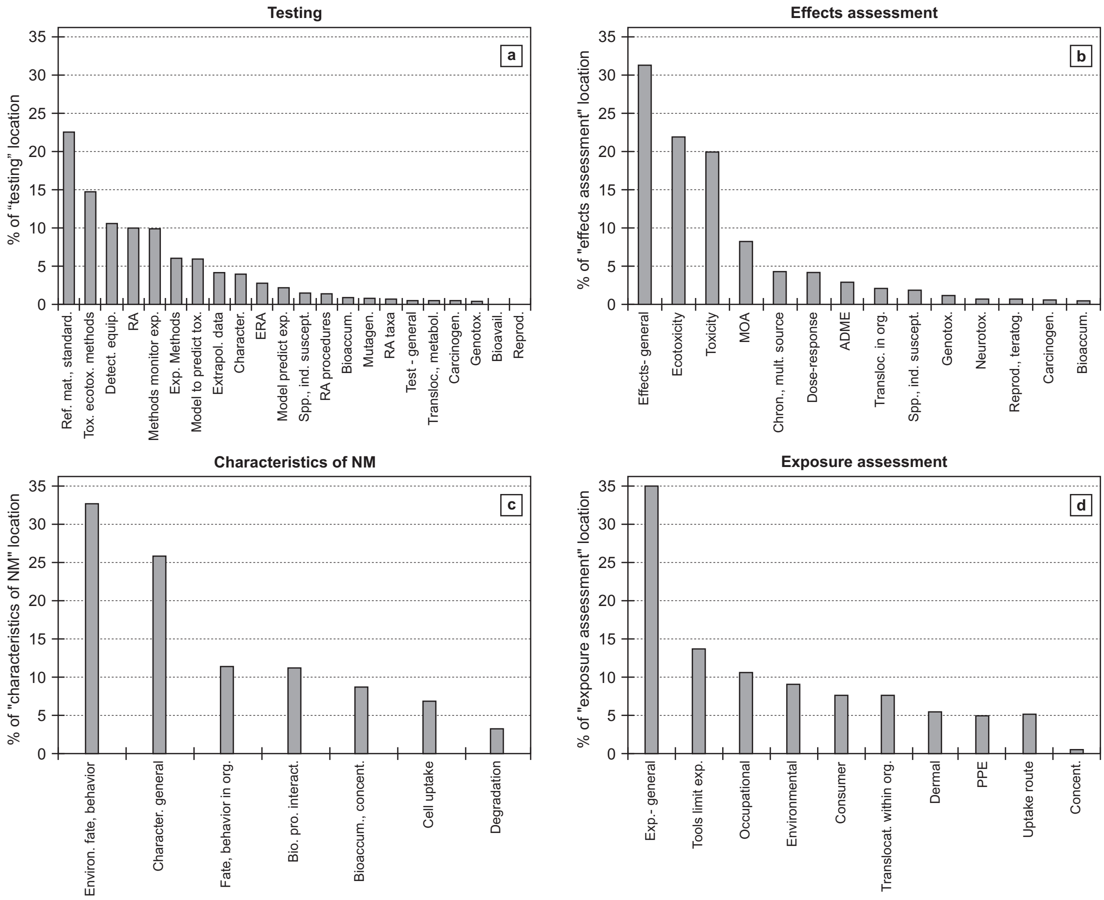


Figure 2. Frequency of occurrence (%) of sub-locations of uncertainty within the four main locations of uncertain (i.e. testing, effects, characteristics, exposure) (Grieger et al. 2009- Paper I).

behavior of NM with 181 citations (e.g. "There are still too many unknowns on how physical-chemical properties may influence behavior of nanomaterials in the environment," Environmental Defense and Dupont 2007a); iv) uncertainty within environmental effects or ecotoxicity of NM with 154 citations (e.g. "Currently, there is a lack of knowledge about these [nano-] products that will need to be addressed before scientists can adequately address environmental health concerns," Goldman and Coussens 2005); v) uncertainty within general aspects of characterizing NM with 143 citations (e.g. "Government authorities and others have identified property characterization...as essential areas in which further research is needed in order to develop risk-management frameworks" Environmental Defense and Dupont 2007a).

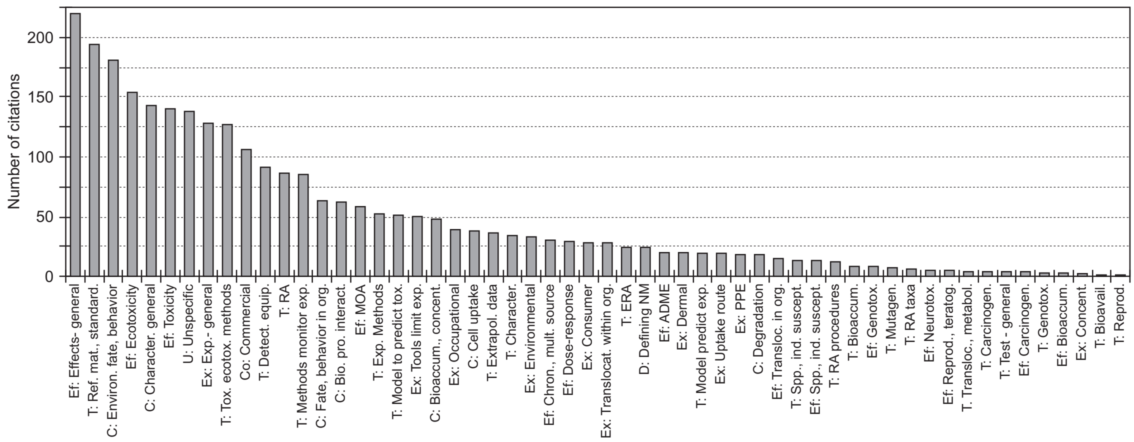


Figure 3. Number of citations for each identified sub-location of uncertainty pertaining to the potential EHS risks of NM as identified by Grieger et al. (2009-Paper I).
C, characteristics of NM; Co, Commercial-related uncertainties; Ex, exposure assessment; Ef, effects assessment; T, testing parameters; U, unspecific uncertainties.

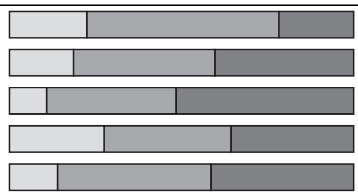
At the same time, the least frequently cited sub-locations were those which referred to a lack of knowledge within the details of specific toxicity testing considerations (e.g. carcinogenicity- or bioavailability testing) as well as within specific effects (e.g. neurotoxicity, reproductive toxicity). This is most likely due to the focus of the selected literature, which excluded for instance scientific journal articles presenting primary or original results from laboratory experiments, as well as the state of knowledge at the time of the analysis on specific effects rather than more general effects within toxicity or ecotoxicity. In addition, it was surprising that more references to a lack of knowledge pertaining to bioaccumulation and persistency and potential effects from these occurring were not more frequently included, especially in light of knowledge on persistent organic pollutants (POPs) (European Union 2006). It was also surprising that there were not more references to the lack of knowledge regarding consumer exposures to NM given their increasing use in consumer products and applications.

This information presented thus far indicates that at the time of the analysis there were relatively well acknowledged areas of uncertainty within not only environmental and human effect and exposure assessments of NM but also within related test methods and equipment- hence, the basic knowledge of the potential EHS risks of NM. Subsequent to April 2008, there have been a number of additional reports and analyses published which have identified known knowledge gaps and critical research needs in the field of EHS risks of NM, many of which have produced consistent findings with this analysis (Aguar and Murcia 2008; SCENIHR 2009; Stone et al. 2010). However, no other studies attempted to rank the areas of uncertainty according to how often they have been cited as important knowledge gaps, although some studies have categorized research needs according to their suggested short- and long-term implementation (Maynard 2006a). Research within the areas of bioaccumulation and persistency of NM have received a bit more attention in the last few years however, albeit still extremely limited (Stone et al. 2010), while research within estimating consumer exposures to NM is still significantly lacking.

Level: The average level of uncertainty across all locations was estimated to be between 2 (medium uncertainty) and 3 (high uncertainty) on a 3-point scale (Table 2). This also fell between 'scenario uncertainty' and 'recognized ignorance.' The location with the lowest relative degree of uncertainty was testing considerations, as it represented >25% of total citations in the analysis and therefore was assigned a value of '1.' The locations of characteristics of NM and effects assessment both had between 15 and 25% of the total citations of uncertainty in the analysis and therefore were assigned a value of '2.' The locations of exposure assessment and 'other areas' (which comprised of defining NM, commercial-related, and unspecific uncertainties) had the highest relative level of uncertainty since they comprised <15% of total citations in the analysis and therefore were assigned a value of '3.'

These results imply that at the time of the analysis the identified locations of uncertainty within the potential EHS risks of NM were likely to be at an early stage of knowledge, related to known potential outcomes but unknown probabilities of these outcomes. It is also likely that the levels of uncertainty for some NM may have been greater or less compared to others, since some NM have been more intensely studied than others (e.g. TiO_2, nano-Ag). Even subsequent to this analysis, it is not expected that the level of uncertainty has significantly altered from these findings based on results presented in several recent reviews of the literature within this field (SCENIHR 2009; Aitken and Ross 2010; Stone et al. 2010; Wise et al. 2010).

Table 2. Level and nature of identified locations of uncertainty within potential EHS risks of NM (Grieger et al. 2009- Paper I).
Level of ‘1’ (low uncertainty) was assigned to locations with >25% of total uncertainty citations in the analysis, ‘2’ (medium uncertainty) to 15-25%, and ‘3’ (high uncertainty) to <15%. Statistical uncertainty: known outcomes and probabilities; scenario uncertainty: known outcomes and unknown probabilities; recognized ignorance: unknown outcomes and probabilities. Epistemic nature: uncertainty which can be reduced with additional research and knowledge; stochastic uncertainty: uncertainty inherent in the system. *“Other areas” refer to the combination of the locations “defining NM”, “commercial-related,” and “unspecified” uncertainty.

Location		Level		Nature	
	% of total	Score		Epistemic	Stochastic
Characteristics of NM	21	2		X	
Effects assessment	25	2		X	X
Exposure assessment	13	3		X	X
Testing considerations	31	1		X	
Other areas*	10	3		X	

= Statistical uncertainty; = Scenario uncertainty; = Recognized ignorance

Nature: Most of the uncertainty in the identified locations was identified as epistemic with the exception of exposure and effect assessments, which are also partially stochastic in nature due to the inherent sources of stochastic variability that often exists in natural systems. This indicates that further research is likely to reduce most of the uncertainty within these locations, primarily due to the widespread recognized uncertainty within the potential EHS risks of NM as documented in the screened literature. In these regards, further empirical efforts are considered to be effective in reducing many of these uncertainties, and which may be similar to investigating the potential risks of other contaminants in natural systems.

2.3.3 Study limitations

It is acknowledged that there may be a number of study limitations in this analysis. First, the identified areas of uncertainty (locations) may not necessarily reflect all EHS-related uncertainty in regards to NM. This is primarily due to the methodology used which attempted to reflect the main areas of uncertainty according to the current state of knowledge as reflected in the screened literature at the time of the analysis (i.e. ‘known unknowns,’ as opposed to ‘unknown unknowns’). In relation to this, it is recognized that the screened literature focused mainly on broad aspects within EHS risks of NM and was not intended for in depth coverage of, for example, specific testing methodologies. Therefore, the screened literature may have influenced the results although it was considered to be relatively representative of state-of-the-art knowledge regarding the EHS risks of NM as a whole. There may also be limitations regarding the estimations of the levels of uncertainty, as estimating states of knowledge may be debatable in itself. For instance, past experiences have shown that increased knowledge may reduce some uncertainties while also revealing previously unknown knowledge gaps (Gee 2009), and hence there are challenges within assessing the 'true' state of uncertainty or knowledge.

2.4 Main findings for uncertainty within nanomaterial risks

- A comprehensive recognition of the scientific uncertainty within the potential EHS risks of NM is important to consider for a number of reasons, particularly: i) uncertainty may ultimately result in unrealized benefits of NM and nanotechnology, and ii) more descriptive information of uncertainty may help minimize potential health or environmental risks while aiming to reap the potential benefits of NM development

- To date, the predominant method to address these various uncertainties has mainly been the description or listing of various knowledge gaps. There have also been a few studies which attempt to specifically assess or handle the uncertainty within the potential EHS risks of NM, most of which have been in conjunction with efforts that involve NM risk analyses or estimates

- Given the importance of uncertainty and considerable data gaps, Grieger et al. (2009) characterized and described the scientific uncertainty of EHS risks of NM using the qualitative-based Walker and Harremoës (2003) framework.

- Based on a thorough literature review, results showed that there are extensive knowledge gaps in nearly all aspects of basic EHS knowledge of NM risks. It was also found that the level of knowledge is likely to be at an early stage, related to known potential outcomes but unknown probabilities of these outcomes. Finally, the estimated nature of uncertainty is mainly epistemic, indicating that further research efforts will likely reduce most uncertainties

3 Assessing environmental risks of nanomaterials

As scientists, regulatory agencies, governments, and organizations attempt to assess the potential environmental risks of NM, it has become clear that there are many significant challenges and hurdles to these assessments. One of the main obstacles in this field is whether standard environmental risk assessment frameworks are suitable for NM or whether other approaches may be needed. However thus far, there is relatively little information available regarding the suitability or robustness of these alternative approaches for NM. The following chapter therefore aims to first review the current status of environmental risk assessment for NM based on standard assessment frameworks, and then subsequently evaluate a number of alternatives frameworks. Similar to other chapters in this thesis, "environmental risks" primarily refer to ecological risks associated with NM present in the environment with some overlap to human exposure to NM through environmental settings due to the inevitable link between the environment and human health.

3.1 Standard approaches

The traditional approach used to assess the potential environmental and health risks of bulk chemicals, namely the chemical risk assessment framework, has been the predominant method employed thus far to assess the potential risks of NM (Rocks et al. 2008; Hansen 2009). As this framework is relatively well-developed, familiar to many stakeholders, and often has regulatory implications (Abt et al. 2010), it has been a logical starting point for NM environmental and health risk assessments (Grieger et al. 2010b – Paper II in Appendix). The following section provides a brief overview of chemical-based risk assessment, primarily within a European context, in order to frame subsequent evaluations and discussions of alternative approaches to this.

The overall purpose of the chemical risk assessment framework is to estimate a possible risk which results from a chemical agent (Renn 2008). Although it may be defined in slightly different ways by different authorities, risk assessment according to the European Commission consists of four main steps: i) hazard identification, ii) dose (concentration) – response (effect) assessment, iii) exposure assessment, and iv) risk characterization (European Commission 2003; European Chemicals Agency 2010a). These same basic steps are also used for environmental risk assessment with the main purpose of addressing potential environmental impacts of substances through performing exposure assessments, which may result from discharges or releases in to the environment, as well as effect assessments on a variety of environmentally-relevant organisms. In these assessments, different environmental systems are considered such as aquatic compartments (freshwater, marine), sediments, terrestrial and air compartments, and micro-organisms in sewage treatment plants (European Chemicals Agency 2008). Final evaluations are then based on outcomes of three main examinations, including i) comparison of Predicted Environmental Concentrations (PEC: expected concentrations of a substance in the environment) to Predicted No Effect Concentrations (PNEC: concentrations below which unacceptable effects are not expected to occur), ii) qualitative environmental risk assessment for cases where quantifying exposure and/or effects is not feasible, and iii) persistency, bioaccumulation, and toxicity (PBT) analyses combined with source and emission evaluations (European Commission 2003; ECHA 2010a, ECHA 2010b).

The aim of the hazard identification step is to identify the effects of a substance of concern, or NM in this case. It is usually based on the inherent physical, chemical, biological, and toxicological properties of a substance. Dose (concentration) - response (effect) assessments aim to estimate PNECs, which are usually derived from single species laboratory testing and when possible established effect and/or no-effect concentrations from model ecosystem tests. PNECs can also be derived by using assessment factors or even with statistical methods if sufficient data exists. The third step, environmental exposure assessment, is derived from measured data and/or model estimations in order to estimate PEC. Data related to exposure patterns or similar use patterns of analogous substances may also be used in this step. These three preceding steps are compiled in the final step, risk characterization, to generate either a quantitative or qualitative risk characterization. Quantitative risk characterization involves a comparison of the PEC with the PNEC for each environmental compartment, and if this can not be performed due to e.g. data gaps then a qualitative risk characterization is performed. For quantitative risk characterization in general, if PEC/PNEC ratio is < 1 then no further testing or risk reduction measures are needed, whereas if PEC/PNEC ratio is > 1 further testing/information or risk reduction measures may be needed. Eventually the

PEC/PNEC ratio should be < 1, which may be achieved through further testing, information gathering, or risk reduction measures.

In Europe, these steps and methodologies for their completion are outlined in a series of documents within "Guidance on Information Requirements and Chemical Safety Assessment" by the European Chemicals Agency (2010a). These are "guidance" documents which outline the processes within (environmental) risk assessment as well as specific testing guidance. Similar authorities in other countries have also published documents which outline procedures used in environmental (or ecological) risk assessment, such as the Environmental Protection Agency in the US (US EPA 1998).

Based on the results of the environmental risk assessment, regulators and/or decision makers will then make subsequent decisions regarding the environmental risks of the substance(s) in question. This interaction of risk assessment and decision making is a complex process, and in most cases there are also other factors involved in environmental health decisions including e.g. cost and public acceptance of risks. In fact, the role of decision making in risk assessment has been subject to intense debate among scientists, regulatory bodies, and organizations (Martuzzi and Tickner 2004; Carolan 2007; Kapustka 2008; The National Academies of Science 2008; Wallace 2008). These debates are still on-going for bulk chemicals as well as NM. Moreover, in cases with extensive uncertainties as in the case of environmental risks of NM, decision making becomes even more challenging. This has been demonstrated in previous and on-going discussions and debates regarding issues such as climate change and genetically-modified crops.

To date there has not been a consistent approach to environmental decision making under extreme uncertainties particularly on an international scale, although there have been some strategies proposed such as Precautionary Principle (European Commission 2000), Weight of Evidence e.g. (van der Sluijs et al. 2008), as well as formal quantitative methods (Saltelli 2002). (Refer to Chapter 2 for more information on uncertainty and its role in EHS risks of NM.) While the challenge of decision making under uncertainty in regards to environmental (or health) risks is not necessarily new (Collingridge 1980; EEA 2001), it is expected to be even more challenging for NM given their diversity and potentially ubiquitous nature (Grieger et al. 2010b – Paper II). As a response, some have questioned whether the risk assessment framework is in fact the most appropriate tool to advise decision making under extensive uncertainty or whether other approaches, such as risk governance mechanisms, may be better suited for these challenges (Brown 2009; Grieger et al. 2010b – Paper II). This subject will be revisited in later sections.

3.2 Environmental risk assessment for nanomaterials

While there has been steady progress made within the fields of nanotoxicology and nanoecotoxicology in recent years (e.g. US EPA 2007; NNI 2008; OECD 2010; Aitken et al. 2009), the presence of large data gaps and significant uncertainties have resulted in the inability to successfully complete risk assessments based on standard approaches. For instance, Hanai et al. (2009), Kobayashi et al. (2009), and Shinohara et al. (2009) published preliminary risk assessments (termed 'interim reports') for TiO_2, CNT, and C_{60} nanoparticles respectively in March 2009. In these reports they concluded that "Currently, with limited available data, it is not possible to develop hazard assessment and exposure assessment applicable to all the various scenarios." In addition, Stone et al. (2010) also published preliminary environmental and health risk assessments for a select number of nanoparticles (fullerenes, CNT, Ag, TiO_2, ZnO). These authors also cited that it was not yet possible to do complete risk assessments due to severe knowledge gaps, and further stated that the assessments were a scientific exercise "which allows the exploration of key questions associated with the risk assessment of nanomaterials, and should not be used in any other way" (Stone et al. 2010).

There are indeed many challenges to performing environmental risk assessment for NM, and many different scientists and organizations have listed these challenges along with corresponding research needs in this field, e.g. (Baun et al. 2008; Navarro et al. 2008; Aitken et al. 2009; SCENIHR 2007, 2009; Hartmann and Baun 2010). However, despite these challenges and limitations of using the standard risk assessment framework as the main tool to assess the environmental (and health) risks of NM, the general consensus from scientists, regulatory agencies, governing bodies, and other organizations has been that this framework can and should be modified for NM (Grieger et al. 2010b – Paper II). For instance, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that despite a number of serious limitations and the fact that the risk assessment framework is still under development, it is nonetheless still applicable to NM (SCENIHR 2009). Similar conclusions have been drawn by other authorities such as the European Food Safety Authority (EFSA), stating that despite many major challenges within the risk assessment framework it was still considered to be applicable for NM in food and feed applications (EFSA 2009). Due to the challenges of performing risk assessments, both SCENIHR and EFSA recommended that risk assessments be performed on a case-by-case basis, which has also been recommended by other scientists (e.g. Stone et al. 2010).

Grieger et al. (2010b- Paper II) also demonstrated that past and current research efforts appear to be framed within standard risk assessment approaches. Through a snapshot of published peer-reviewed journal publications, research projects, and public funding within the nano-risk field, Grieger et al. (2010b- Paper II) documented that, perhaps not surprisingly, most scientific research has indeed been directed to fit within the chemical-based risk assessment paradigm (as opposed to broader issues of decision support, risk governance, management, and monitoring) (Figure 4). It should be noted that this analysis did not attempt to provide a complete analysis of research publications and projects within the field, but rather to provide a synopsis of the general direction and distribution of research efforts to date.

This analysis also found that these patterns are not likely to change in the near future given the distribution patterns of national and international funding schemes. For instance, research funds have been mainly directed towards improving technical knowledge or developing new test protocols and equipment for NM (Aguar and Murcia 2008; NNI 2008) – hence, research that is most likely geared towards fitting with the risk assessment paradigm. These findings demonstrate that not only has research within the nano-risk field been largely directed towards ultimately fulfilling the risk assessment framework thus far, but it is also likely to continue in this direction as research continues with the aim of assessing the environmental and health risks of NM.

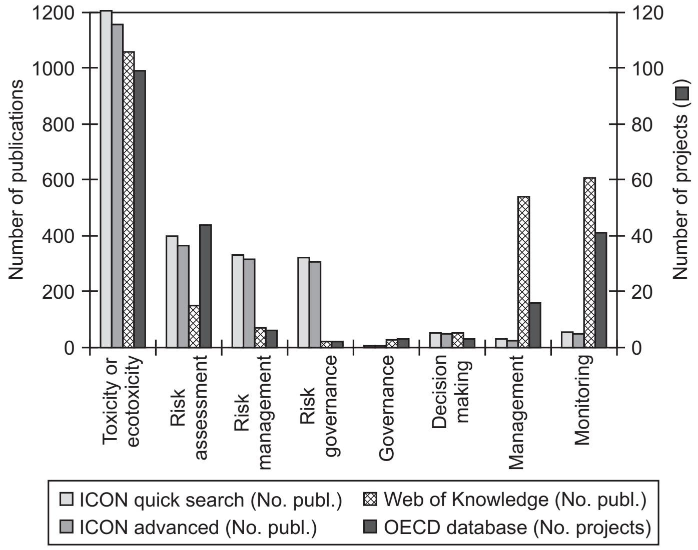


Figure 4. Number of scientific journal article publications and research projects within nano-risk topics and EHS issues of NM (Grieger et al. 2010- Paper II).
The analysis was performed by reviewing the ISI Web of Knowledge and International Council on Nanotechnology (ICON) Virtual Journal (using both 'quick' and 'advanced' search options) to search for journal publications and the Organisation for Economic Co-operation and Development (OECD) NM risk research project database for completed or on-going research projects. Searches were made within all years, and databases were accessed 30 June 2009. The following search terms were used within the 'topic' fields of the database search engines: 'toxicity', 'ecotoxicity', 'exposure', 'risk assessment', 'risk management', 'risk governance', 'decision making', 'management' and 'monitoring.' Unlike the ICON and OECD databases, the ISI Web of Knowledge database was not confined to NM risk research and therefore the previously cited search terms were used together with 'nanotechnology', 'nanomaterial' or 'nanoparticle.'

3.3 Challenges and limitations

Among the numerous data gaps and challenges within understanding the potential environmental and health risks of NM, the European Commission's SCENIHR outlined some of the major research needs specifically for environmental risk assessment in their last report entitled "Risk Assessment of Products of Nanotechnologies" (SCENIHR 2009). These included challenges particularly within measuring and characterizing NM in various environmental media; analytical methods to detect and measure concentrations of NM in the environment; modeling environmental concentrations of NM following release; extent or rate of NM dissolution in water; ecotoxicological studies particularly for soil and terrestrial species; the role of dispersants, surfactants, solvents, as well as various coatings in ecotoxicological studies. Many of these same research needs were also identified in a recent analysis (Stone et al. 2010), particularly the lack of measured and modeled exposure data for NM, including the ability to detect nanoparticles in environmental matrices; challenges in determining the influence of nanoparticle size or shape in reference to the ecotoxicity of any group of nanoparticles; lack of data on the influence of coatings; and a particular lack of studies which focused on chronic toxicity to a variety of test organisms (fish, Daphnia, algae, sediment and terrestrial organisms). Similar lists of research needs within the field have also been published by a number of other authors as well as national and international organizations (e.g. Crane et al. 2008; Handy et al. 2008; NNI 2008; Alvarez et al. 2009; Morris et al. 2009; Wiesner et al. 2009).

At the same time it is expected that many of these limitations to performing and completing environmental risk assessment of NM will eventually be overcome with continued research efforts. This is in part due to the mainly epistemic nature of most of the knowledge gaps within the health and environmental risks of NM (RCEP 2008; Grieger et al. 2009- Paper I). In this way, it is expected that through dedicated research efforts and time, methodologies and protocols to carry out risk assessment for NM will progress and eventually e.g. standardized testing methods, analytical tools, NM characterization, and dose-response information will be developed (ISO 2008, 2010; OECD 2008, 2009a, 2009b, 2010).

However the main caveat of this progress is that its development is likely to be resource- and time- demanding. For example, it has been estimated that testing of currently existing nanoparticles in the US alone may cost \$249 million - \$1.18 billion and take 34-53 years (Choi et al. 2009). Other scientists and organizations have also estimated that at least a decade was needed in order to obtain critical knowledge within the field of EHS risks of NM (e.g. Maynard 2006a; RCEP 2008), while others also noted the expected time- and resource- consuming fate of NM testing (Morgan 2005; Hansen 2009). Moreover, the history of bulk chemicals and other substances have also revealed that time was in fact needed to develop new knowledge and then develop and apply regulatory test methods, as in the case of endocrine-disrupting chemicals (Sumpter and Johnson 2008; OECD 2009a, 2009b). As expressed by The UK's Royal Commission on Environmental Pollution (RCEP), "So far, only about 3,000 of the 30,000 bulk chemicals in common use in the EU have been formally assessed for health and environmental effects…Unless there are orders of magnitude increases in efforts to test new nanomaterials coming onto the market, it will be many years before toxicity test data become available for the manufactured nanomaterials that are currently in use or which are under development” (RCEP 2008).

This process of data acquisition followed by developed test guidelines is most likely already in progress for NM. For example, the Organisation for Economic Co-operation and Development (OECD) has already identified some test guidelines which appear to be adequate for NM physico-chemical properties while others appear to be inadequate for NM (OECD 2009b). However, developing adequate knowledge in order to assess the environmental risks of NM is made more complicated and challenging given the diversity of NM as well as the applications in which they are found. The fast pace of NM development also further hampers these challenges. Therefore, given these challenges and limitations, the standard approach for environmental risk assessment for NM appears to be limited particularly for near-term assessments largely due to the time and resources needed to acquire meaningful results (Grieger et al. 2010b – Paper II).

Other scientists and organizations have also expressed doubt regarding the ability of traditional risk assessment frameworks to adequately assess the environmental (and health) risks of NM (RCEP 2008; Hansen 2009; Linkov et al. 2009a; Metcalfe et al. 2009). For instance, Stone et al. (2010) recently concluded that “it seems that currently available test methods and risk assessment methodologies might not be sufficient to effectively assess the possible risk of nanomaterials.” Similarly, Hansen (2009) also expressed serious doubts regarding the applicability and suitability of the risk assessment framework for NM, citing numerous limitations within all stages of the risk assessment framework and challenges due to the fact that fulfilling the framework is likely to be time- and resource- demanding using a case-by-case approach. Specifically in relation to the environment, Metcalfe et al. (2009) concluded that “Traditional risk assessment procedures are inadequate for predicting the ecological risks associated with the release of nanomaterials (NM) into the environment” and that the “pace of development of NM will exceed the capacity to conduct adequate risk assessments using current methods and approaches.” Linkov et al. (2009a) also concluded that “traditional risk assessment procedures are inadequate for predicting the ecological risks associated with the release of nanomaterials.”

3.4 Alternatives to standard approaches

As a response to these previously described limitations regarding the suitability and utility of the traditional risk assessment framework for NM, a number of scientists and organizations have proposed that perhaps other frameworks, tools, and approaches may be better suited for the complex risks of NM. Some of these are techniques or methods which may be used within other NM risk analyses, estimates, or decision making aspects, and therefore are complimentary to other frameworks or approaches. For instance, expert elicitation (Morgan 2005; Wardak et al. 2008) and Weight of Evidence (WOE) (Linkov et al. 2007, 2009b) have both been proposed to help compensate for large data gaps, and in the case of WOE also in decisions involving conflicting evidence. Adaptive management has also been proposed in order to help create more flexible and iterative processes (Davis 2007; Linkov et al. 2007), while Alternative Assessments (Raphael 2009) may aid in choosing 'safer' alternatives in cases of uncertain NM risks. Hansen et al. (2008) also developed a categorization framework to identify exposure potentials based on the physical location of the NM in an application (e.g. surface-bound, embedded).

At the same time others have proposed broader, more fundamental mechanisms should be used prior to NM development. For instance, real-time technology assessment has been suggested to help aide the responsible development of NM during innovation processes rather than in the post-development phase (Guston and Sarewitz 2002). Grieger et al. (2010b –Paper II) also propose that research should be dedicated to developing adaptive and responsive risk governance mechanisms for NM, specifically focusing on timely yet informed decisions under uncertainty. This was in light of a major challenge for traditional risk assessment; specifically the need for timely decisions under uncertainty as noted by several authors (RCEP 2008; Brown 2009; Owen et al. 2009).

Meanwhile, a number of other frameworks and tools designed to assess, analyze, or estimate NM health and environmental risks have also been proposed for NM which may serve as alternatives to the standard risk assessment framework (e.g. Nano Risk Framework, Comprehensive Environmental Assessment (CEA), Multi-Criteria Decision Analysis (MCDA)). In fact, Grieger et al. (2010- Paper III in Appendix) identified four main categories of these alternative frameworks as further discussed below (section 3.5): risk governance frameworks, risk assessment and management frameworks, screening-level frameworks, and adaptable risk assessment tools. However, it is still unclear which of these alternative frameworks may be most effective or best suited to handle the complex environmental risks of NM. In response, a number of scientists and organizations have recommended that more research should be dedicated to investigating these alternative approaches to standard risk assessment, including the identification of their strengths and weaknesses and their suitability for NM (Rocks et al. 2008; Grieger et al. 2010b– Paper II; OECD 2010; Stone et al. 2010; Wise et al. 2010).

3.5 Critical evaluation of risk analysis frameworks

In a systematic review and evaluation, Grieger et al. (2010- Paper III) assessed and evaluated various frameworks that have been proposed by large organizations or regulatory bodies for NM risk analysis which may serve as alternative to standard risk assessment. This analysis focused primarily on environmental risk analysis of NM, but due to the scarcity of frameworks which had a specific focus on environmental aspects, also opened up to include frameworks that have been proposed for NM health risk contexts. These frameworks were assessed according to a number of criteria (10 in total) which have been cited as important for successful implementation of NM analysis. The analysis did not, however, aim to e.g. rank the superiority of the alternative frameworks in relation to each other. This was because many of the frameworks differed in scope and objectives and direct comparisons to each other may produce misleading results.

3.5.1 Methodology

The following frameworks were selected for evaluation:

- *International Risk Governance Council (IRGC) Risk Governance Framework*: (IRGC 2005, 2007, 2009)
- *Comprehensive Environmental Assessment (CEA)*: (Davis 2007; Anastas and Davis 2010; US EPA 2009, 2010a, 2010b)
- *Nano Risk Framework*: (Environmental Defense and Dupont 2007a, 2007b, 2007c, 2007d)
- *Nano Screening Level Life Cycle Risk Assessment framework (Nano LCRA)*: (Shatkin 2008, 2009a, 2009b)
- *Multi-Criteria Decision Analysis (MCDA)*: (Linkov et al. 2007; Seager and Linkov 2008; Tervonen et al. 2009; Canis et al. 2010)

- *CENARIOS® (Certifiable Nanospecific Risk Management and Monitoring System)*: (TÜV SÜD 2008; Bühler Partec 2010; Swiss Federal Office for the Environment 2010)
- *Precautionary Matrix*: (Höck et al. 2008, 2010; Swiss Federal Office of Public Health 2010)
- *XL Insurance Database Protocol* (Robichaud et al. 2005)

These frameworks were evaluated against the following criteria which have been cited as important parameters for inclusion in environmental and health risk analysis of NM.

1. *Flexible for variety of nanomaterial*s: Due to the extensive diversity of NM and applications containing them, a risk analysis framework should be able to be suitable for different variations of NM (Oberdörster et al. 2005; Owen and Handy 2007; RCEP 2008)

2. *Suitable for multiple decision contexts*: A risk analysis framework should be able to be suited for different decision contexts, such as different receptors or decision-making contexts (RCEP 2008; The National Academies of Science 2008)

3. *Incorporate uncertainty analysis*: Scientific uncertainty is a significant factor in analyzing environmental NM risks. Therefore frameworks should be able to actively acknowledge, identify, and incorporate uncertainty analyses as an approach to better deal with these uncertainties (DEFRA 2007; Dale et al. 2008; van der Sluijs et al. 2008; Wiesner et al. 2009)

4. *Include life cycle perspectives*: It is generally accepted that the potential environmental and health risks of NM should be assessed over the life cycle of a NM or nano-product (The Royal Society and Royal Academy of Engineering 2004; Council for Science and Technology 2007; DEFRA 2007; RCEP 2008; US EPA 2008)

5. *Ability to be iterative or adaptive*: Especially given the early state of knowledge regarding NM and frameworks for their assessments, a risk analysis framework should be able to be iterative or adaptive to new information (Owen and Handy 2007; RCEP 2008; The National Academies of Science 2008)

6. *Enable more timely decision making*: Due to the often lengthy processes involved in acquiring data and making subsequent decisions as well as the rapid pace of NM innovation, a framework should help support timely yet informed decision making (Collingridge 1980; RCEP 2008; Owen et al. 2009)

7. *Transparent in objectives, steps for completion, and application*: A framework for NM risk analysis should be transparent in its objectives, steps for completion, as well as application, especially if third-parties should be able to use or apply the framework to various NM or NM applications (Owen and Handy 2007; The National Academies of Science 2008; Center for International Environmental Law 2009)

8. *Ability to integrate various stakeholder perspectives*: Stakeholder perspectives and needs are important to include in a framework in order to help ensure correct problem formulations in societal contexts, and which may also help avoid lengthy debates and discussions (US EPA 2007; David 2008; Dale et al. 2008; The National Academies of Science 2008)

9. *Ability to integrate precaution*: Given the extensive uncertainties pertaining to the potential environmental and health risks of NM, it has been suggested that precautionary measures may be included in a risk analysis framework (Martuzzi and Tickner 2004; Environment Agency 2008; Murashov and Howard 2009). This may serve as a safety measure until more comprehensive information is available. "Precaution" generally refers to an action or measure to avoid possible adverse effects and is not directly in reference to the Precautionary Principle (European Commission 2000)

10. *Ability to include qualitative or quantitative data*: Due to the extensive challenges of obtaining high quality quantitative data to assess the potential environmental risks of NM, it may be important for a framework to be able to include both qualitative and quantitative data (The Royal Society & The Royal Academy of Engineering 2004, 2006; SCENIHR 2007; Murashov and Howard 2009)

The authors of the analysis scored the frameworks according to the following. If a criterion was obvious and embedded in the framework and demonstrated in application, "full credit" was given which was denoted by 'X.' If a criterion was included only to some extent or to a lesser degree or not fully demonstrated in application, “partial credit” was given as denoted by ‘x.’ If a criterion was not directly included in a framework but could be easily adapted or included in the framework as demonstrated through application, it was scored as ‘A’ to denote its adaptability for this criterion. Finally, if a criterion was not included from a framework, its absence was denoted by ‘-,’ and ‘N/R’ was given in cases where a framework was not intended to include a specific criterion.

Prior to the final scoring of each framework, the authors of the frameworks were also contacted and requested to evaluate their own framework according to the criteria without prior knowledge of how their framework was initially scored by the authors of the analysis. This was intended to gather any additional knowledge pertaining to e.g. previously unknown literature or data regarding the selected frameworks. Taking into account the responses from the authors, a final scoring evaluation was made by the authors of the analysis. This was subsequently made available to the authors of the frameworks in which they were given the opportunity to respond if necessary. This served as a dialogue-format to gather as much information as possible regarding the selected frameworks and their demonstrated applications to NM. The authors of the frameworks were only able to view and respond to the results of their own framework.

3.5.2 Results and discussion

3.5.2.1 Overview of frameworks

The investigated frameworks varied (significantly, in some cases) in terms of their objectives and scope. In fact, four main categories of frameworks were identified: risk governance frameworks, risk assessment and management frameworks, screening-level frameworks, and adaptable risk assessment tools.

Risk governance frameworks. The IRGC’s Risk Governance Framework is a comprehensive risk governance framework which incorporates many societal aspects (IRGC 2005). It is primarily intended for policy makers and regulators in governance agencies and risk managers in industry or large organizations. CEA also a comprehensive risk framework which combines risk analyses with decision support, and has been proposed to identify a range of potential impacts over a life cycle of a NM or product as well as prioritize research areas (Davis 2007). Although it is not intended to specifically cover risk governance aspects directly, input from a range of stakeholders and experts may also be used. Both

IRGC's Framework and CEA were first developed for other environmental and health risk contexts and subsequently applied to NM (IRGC 2009; US EPA 2009, 2010a, 2010b).

Risk assessment and management frameworks. The Nano Risk Framework is a comprehensive assessment and management framework that aims to characterize and describe the potential health and environmental risks of a NM or nano-application over its lifecycle (Environmental Defense and Dupont 2007a). It consists of a user-friendly manual equipped with tables and instructions for use. To date, it has been applied to three different case studies thus far (Environmental Defense and Dupont 2007b-d). CENARIOS is also a risk assessment and management framework as well as a certification tool and system (TÜV SÜD 2008). It is intended primarily for industry to assess and manage the potential risks of NM mainly in occupational settings. To date, it has been applied to various metal oxide dispersions in different solvents at Bühler Partec in Switzerland (although no specific information regarding these could be provided due to company confidentiality reasons) (Widmer 2010- personal comm.; Homman 2010- personal comm.).

Screening-level frameworks. The Precautionary Matrix is a screening-level risk analysis and management frameworks which evaluates potential sources of NM risks using various criteria (Höck et al. 2008, 2010). It is a very structured and automated tool which a user can fill out based on available knowledge of a NM or nano-product, and is primarily intended for (occupational) risk assessors in trade and industry. To date, it has been applied to a variety of NM and NM-products, although details of these have been mostly unavailable due to company confidentiality reasons (Swiss Federal Office of Public Health 2010; Höck 2010- personal comm.). Nano LCRA is also a screening-level tool to identify the potential risks over a nano-product's life cycle, and also has been proposed to help prioritize research priorities (Shatkin 2008). However, concrete information regarding the details of completing Nano LCRA for specific NM or applications have not been yet available. Thus far, it has only been theoretically applied to a few NM or applications (Shatkin 2009a, 2009b).

Adaptable risk assessment tools. MCDA and XL Insurance Database Protocol are both specific methods and tools which have been previously developed for other risk contexts and proposed for NM. MCDA is actually a range of decision support tools in which various criteria are selected, ranked, and used to compare alternatives (Linkov et al. 2006, 2007). Tervonen et al. (2009) used MCDA to rank the relative risks of different nanoparticles, and Canis et al. (2010) also used MCDA to rank different NM manufacturing methods. XL Insurance Database Protocol is a tool originally developed to estimate and rank risk candidates and subsequently calculates insurance premiums. Robichaud et al. (2005) applied the XL Insurance Database Protocol to rank the relative risks of different methods to manufacture five nanoparticles.

3.5.2.2 Scoring of frameworks against criteria

An overview of the evaluation of the investigated frameworks according to the criteria is presented in Table 3. For more specific details and supporting information regarding this evaluation, refer to Grieger et al. 2010- Paper III in Appendix.

1. *Flexible for variety of NM*: All frameworks were suited for a variety of nanomaterials, and which was also confirmed in documented applications.

2. *Suitable for multiple decision contexts*: Nearly all of the frameworks were suitable for multiple decision contexts. Five out of 8 of these received 'full credit' for this criterion, as this was also demonstrated in applications (IRGC, CEA, Nano Risk, LCRA, MCDA). Two frameworks received partial credit since it was present in theory but not well demonstrated in applications (CENARIOS®, XL Insurance). This criterion was absent from the Precautionary Matrix, as this framework contained pre-determined objectives rather than being able to be adapted to different decision contexts.

3. *Incorporate uncertainty analysis*: Most of the frameworks (5 out of 8) met this criterion at least to some extent, and MCDA demonstrated this both in theory and applications. However, IRGC, CEA, Nano Risk, LCRA received partial credit for this criterion since uncertainty was handled primarily through the identification of 'known unknowns' and data gaps, very qualitative, or was not well demonstrated in applications. Some frameworks did not meet this criterion in theory or applications (CENARIOS®, Precautionary Matrix, XL Insurance).

Table 3. Evaluation of selected frameworks that have been proposed by large organizations or regulatory bodies for environmental risk analysis of nanomaterials (NM) according to various criteria (Grieger et al. 2010- Paper III).

Note: literature documenting theory and applications range from peer-reviewed journal articles (*) to organizational reports (**) and other non-peer reviewed material (***) (e.g. presentation slides, webpage, book chapter).

X = criterion is obvious and embedded in the framework and demonstrated through application;
x = criterion is included to some extent or to a lesser degree or not fully demonstrated in application;
A = criterion is not directly included in the framework but can be easily adapted or included and which has been demonstrated through application;
- = criterion is absent from the framework;
N/R = criterion was not relevant to the framework.
* =Considered or mentioned to be important but not included or integrated in framework specifically

	Criteria									
Framework	1. Variety of NM	2. Multiple decision contexts	3. Uncert. analysis	4. Life cycle perspect.	5. Iterative or adaptive	6. Timely decision making	7. Trans-parent	8. Stake-holders	9. Pre-caution	10. Qual. / quant. data
IRGC Risk Governance Framework**	X	X	x	x	x	-*	x	X	x	X
CEA*,**	X	X	x	X	A	A	x	X	x	X
Nano Risk Framework**	X	X	x	X	X	-*	X	x	X	X
Nano LCRA***	X	X	x	X	x	-	x	-*	x	X
MCDA*	X	X	X	A	A	A	X	A	A	X
CENARIOS®**,***	X	x	-	x	X	A	x	N/R	x	x
Precautionary Matrix **,***	X	-	-	X	A	A	x	N/R	x	X
XL Insurance Database Protocol*	X	x	-	x	A	A	x	N/R	A	X

4. *Include life cycle perspectives*: All of the frameworks considered life cycle perspectives or could be easily amended for this. Half of the investigated frameworks included steps for this in theory and which were also demonstrated in application (CEA, Nano Risk Framework, Nano LCRA, and Precautionary Matrix). Some of the frameworks included life cycle perspectives in theory but did not demonstrated this in application (IRGC, CENARIOS®), while some only included this criterion to some extent (XL Insurance) or could be easily adapted for this although not specifically incorporated into the approach (MCDA).

5. *Ability to be iterative or adaptive*: All of the frameworks were able to be iterative or adaptive or could be easily amended for this. Nano Risk Framework and CENARIOS® had iterative or adaptive elements and which were also demonstrated in application, while IRGC Risk Governance Framework and Nano LCRA presented this in theory but which was absent in documented applications. Some frameworks did not directly contain iterative or adaptive elements but could be easily amended for this (i.e. CEA, MCDA, Precautionary Matrix, XL Insurance), and which was also recommended by some of the authors, i.e. (Davis 2007; Seager and Linkov 2008).

6. *Enable more timely decision making*: None of the frameworks specifically incorporated mechanisms for timely decision making, although most of them (5 out of 8) could be easily amended for this if needed (CEA, MCDA, CENARIOS®, Precautionary Matrix, XL Insurance). This is expected to be highly context dependent. This criterion was mentioned was being important in IRGC's Risk Governance Framework and Nano LCRA although no specific elements were incorporated for this into the frameworks.

7. *Transparent in objectives, steps for completion, and application*: All of the frameworks were transparent to third-parties to at least some extent. The Nano Risk Framework and application of MCDA were the only frameworks which demonstrated this both in theory (in objective and steps for completion) as well as documented applications. All others were either transparent to only some extent or it was not well-documented how transparent the application process was in reality or in documented applications (IRGC, CEA, Nano LCRA, CENARIOS®, Precautionary Matrix, XL Insurance). For example, IRGC's Risk Governance Framework and Nano LCRA were not well-documented for transparency in application due to e.g. lack of structured

formats to follow in execution or e.g. well-demonstrated examples of transparency in this process. Moreover, CEA was transparent in objectives, steps for completion and application, although many details involved in the exact steps needed to fulfill the application (which involve stakeholder collaboration and expert involvement) were not completely clear enough to be adopted by outside third-parties. Other frameworks were difficult to verify transparency in application due to company confidentiality reasons (CENARIOS®, Precautionary Matrix).

8. *Ability to integrate various stakeholder perspectives*: Half of the frameworks integrated stakeholder perspectives or could be easily adapted for this (IRGC, CEA, Nano Risk, MCDA). Nano LCRA did not include this criterion in theory or demonstrated application (although mentioned the importance of stakeholder inclusion), while the other frameworks were scored 'N/R' since this criterion was not relevant or applicable (CENARIOS®, Precautionary Matrix, XL Insurance).

9. *Ability to integrate precaution*: All of the frameworks included precautionary aspects at least to some extent, although not necessarily termed "precaution" or "precautionary." The Nano Risk Framework included precautionary aspect (worst-case assumptions) in theory and demonstrated applications, while IRGC's Risk Governance Framework, Nano LCRA, CENARIOS®, and Precautionary Matrix included precautionary aspects in theory but was not well-demonstrated in documented applications. CEA included precautionary aspects to some extent and verified in applications, through "what if" scenarios, although this was considered to be to a lesser degree. MCDA and XL Insurance Database Protocol were considered to be easily adaptable for this criterion although they did not include precautionary aspects directly.

10. *Ability to include qualitative and quantitative data*: All frameworks except for CENARIOS® were able to include both qualitative and quantitative data, and which was also demonstrated in applications. CENARIOS® included this criterion in theory but was unable to document this in application due to reasons of confidentiality.

This information indicates that most of the investigated frameworks included many if not most of the selected criteria, and hence some of the main parameters considered as important for inclusion in successful (environmental) risk analysis of NM. More specifically, most of the investigated frameworks were i) flexible for multiple NM, ii) suitable for multiple decision contexts, iii) included life cycle perspectives, iv) transparent, v) included precautionary aspects, and vi) able to include qualitative and quantitative data. At the same time, half of the frameworks did not specifically contain elements for iteration or adaptation and none of them contained elements for timely decision making, although most of these could be easily amended for these criteria. Furthermore, it also appears that some criteria were not as fully demonstrated in documented applications as others, such as incorporating uncertainty analyses beyond merely identifying knowledge gaps and transparent documentation of applications.

Additional advantages and limitations. It was also found that further advantages of some of the frameworks included the provision of structured and guided formats (e.g. worksheets, tables) to describe, evaluate, and assess the environmental (and health) risks of NM and which were publically accessible through the internet (i.e. Precautionary Matrix, Nano Risk Framework). Therefore, third-parties could potentially easily understand and use these frameworks and demonstrated applications and potentially apply these to other NM cases if necessary. Meanwhile, other frameworks may also have further advantages of being previously developed and used in other environmental risk contexts, and hence potentially already been undergoing previous reviews and development in regards to the overall risk analysis or assessment approach (i.e. IRGC, CEA, MCDA, XL Insurance). Of course their specific relevance and utility for NM is still not completely clear, as most of these frameworks have only been applied to a very limited number of NM or nano-applications.

Meanwhile, other limitations of many of the investigated frameworks include the fact that most of these are primarily developed and applied for health (occupational) rather than environmental risk contexts. In fact, half of the investigated frameworks were developed primarily for industry and focused on occupational risks of NM (i.e. Nano Risk Framework, CENARIOS®, Precautionary Matrix, XL Insurance), and environmental risks were mainly considered at a very general level and primarily in terms of identifying potential risks related to environmental exposures following e.g. production or manufacturing of NM. Furthermore, it is not clear if the documented applications of the investigated frameworks have been 'successful,' given the extensive uncertainties surrounding the potential environmental risks of NM as well as the lack of benchmarked assessment or analysis tools. Especially for newly developed frameworks which have been specifically developed for NM, it may be difficult to simultaneously test 'new tools' with 'new materials.' Finally, there may also be difficulties in labor-intense processes for frameworks which involve stakeholder involvement (i.e. IRGC, CEA) as well as consistency and reproducibility issues if results are dependent upon e.g. expert groups or panels (i.e. CEA, Nano LCRA, MCDA).

3.5.3 Study limitations

It is recognized that the analysis by Grieger et al. (2010 – Paper III) may have a number of limitations. First, as this analysis attempted to evaluate the investigated frameworks based on currently available and accessible documents, many of these documents were in the form of grey literature, including non-peer reviewed reports, book chapters, and presentation slides. Only in a few cases was peer-reviewed literature in the form of e.g. journal articles available. Furthermore, some of the frameworks were unable to fully demonstrate their applications due to confidentiality reasons. Hence, these may not have received 'full credit' for some criteria and those frameworks which had non-confidential documentation of case studies. This is unfortunate, however as this analysis aimed to evaluate these frameworks according to the literature available to third-parties, in which they may use this information to e.g. perform their own NM risk analyses, this was not possible to overcome in some cases (CENARIOS®, Precautionary Matrix). Furthermore, as all of the frameworks had very limited numbers of documented applications, further advantages and limitations than those reported here may be visible only through additional applications.

3.6 Main findings for risk analysis frameworks for nanomaterials

- The chemical-based environmental risk assessment framework has been the standard approach to assess the environmental risks of NM thus far. While there have been some advances in the field of nano(eco)toxicology, there are still large data gaps and significant uncertainties, resulting in the inability to successfully complete environmental risk assessments

- As a response to limitations of standard risk assessment for NM, a number of different scientists and organizations have proposed that perhaps other methods or frameworks may be better suited for NM risk analysis

- After an evaluation of various frameworks which have been proposed for NM risk analysis, Grieger et al. (2010- Paper III) found that most of these were flexible for multiple NM, suitable for multiple decision contexts, included life cycle perspectives, were transparent, included precautionary aspects, and able to include qualitative and quantitative data. Other key findings include that half of these frameworks did not specifically contain elements for iteration or adaptation and none of them contained elements for timely decision making, although most of these could be easily amended for these criteria

- It was also found that environmental considerations were largely lacking in these frameworks and most of them concentrated on health (occupational) risk contexts. There were also very limited documented applications for specific NM or nano-applications

- As the frameworks ranged from very broad risk governance frameworks to more specific assessment tools, it is likely that they are not all equally applicable or appropriate for a given NM environmental risk context. Therefore, care should be taken when selecting the most appropriate risk assessment or analysis strategy

4 Case study: Environmental risks and decision making for nanomaterials

Among numerous other proposed benefits of using and applying NM, their development and use in environmentally-sustainable products and applications has received increased attention in recent years. For instance, there are a number of nano-applications within the rapidly growing field of renewable energy development, such as hydrogen storage, solar cells, light-emitting diodes, and fuel additives or catalysts (Wickson et al. 2010). Meanwhile, other applications using nanotechnology or NM have been proposed to potentially decrease the production of waste and/or pollution, such as the development of lighter, stronger materials for automobiles and airplanes (Lloyd and Lave 2003). These developments have been in light of increasing concern regarding anthropogenic climate change resulting from emissions of atmospheric carbon and other greenhouse gases. There are also other environmental applications of nanotechnology or NM which directly aim to improve for instance water quality or remediate the environment from soil and water pollution. For example, some nanoparticles have been proposed for water treatment (Theron et al. 2008) while other nanoparticles may be used for soil and groundwater remediation such as the use of zero-valent iron nanoparticles (nZVI). In fact, the use of nZVI has been proposed as one of the most promising nanoparticles for *in situ* environmental remediation in recent years (Grieger et al. 2010a – Paper IV in Appendix).

While many of these nanotechnologies and NM applications have been proposed as sustainable or ‘green’ solutions to a number of environmental challenges that currently exist, it is not yet clear how to fully assess their environmental impacts. This is mainly due to the extensive uncertainties and other challenges of assessing the environmental risks of NM as a whole as detailed in the previous chapters of this thesis. In addition, past experiences with chemicals and other substances have illustrated the need to thoroughly analyze technology options before their full scale introduction in order to avoid the potential for a number of undesirable consequences to occur, such as adverse environmental or health impacts (EEA 2001), costly clean-up efforts (Hansen et al. 2008b), or even cases where one set of risks were substituted with another set (i.e. “risk-risk trade-offs”) such as in the case of methyl *tertiary*-butyl ether (MTBE) (Davis and Farland 2001; Davis 2007; Hansen et al. 2008b). Therefore, it may not yet be fully clear how to comprehensively consider and weigh the potential environmental benefits and largely unknown risks of many of the proposed sustainable or environmentally-beneficial nano-technologies or applications. This may be especially the case if scientists, engineers, and decision-makers rely upon results from standard environmental risk assessments in order to make these assessments, which are currently unable to be completed (see Chapter 3).

Therefore in light of these challenges within environmental risk assessment and decision making for NM, the present chapter aims to apply novel approaches or strategies for decision making regarding the potential environmental risks of select NM. These applications will be primarily based on a case study involving the use of nZVI for *in situ* soil and groundwater remediation. In addition, it is also intended that these demonstrations and information presented may be useful not only for scientists and engineers working with nanotechnologies or NM-embedded applications but also for decision makers involved in assessing the environmental risks of NM and making associated decisions.

4.1 nZVI for *in situ* remediation

Background

The development and use of nZVI for remediating contaminated soil and groundwater has received increasing amounts of attention in recent years, following the use of larger iron particles for remediation purposes. The use of nZVI has been attractive as a remediation technique primarily due to its faster contaminant degradation rates (related to its increased reactivity) (Theron et al. 2008; Karn et al. 2009); wider range of contaminants suitable for degradation (e.g. polycyclic aromatic hydrocarbons (PAHs), pesticides, heavy metals (Li et al. 2006); and broader range of applications associated with direct *in situ* injections, including access to hard-to-reach sites (Elliott and Zhang 2001) and possibility of additional injections (Liu and Lowry 2006). The increased reactivity of nZVI compared to larger iron particles is mainly attributed to an increase in surface area associated with its nano-sized dimensions (Macé et al. 2006).

Numerous studies have documented the rapid degradation of a variety of contaminants using nZVI compared to larger iron particles, e.g. 25 times for hexavalent chromium (Cao and Zhang 2006) and up to 38 times for different polychlorinated biphenyls (PCBs) (Lowry and Johnson 2004). Another main advantage of using nZVI for *in situ* remediation is its potential cost-effectiveness

(Karn et al. 2009), as it is considered to be at least competitive with other alternative *in situ* remediation options such as chemical oxidation, thermal enhanced treatments, stimulated reduction dechlorination, and monitored natural attenuation (Grieger et al. 2010a- Paper IV). Other cited advantages include decreased environmental disturbances related to its *in situ* applications (e.g. elimination of excavations, Karn et al. 2009), the possibility of enhancing on-site anaerobic microbial growth and natural biodegradation (Henn and Waddill 2006), as well as the production of less toxic intermediate degradation products compared to using larger iron particles (Choe et al. 2001).

nZVI properties and characterization

nZVI is essentially nano-sized iron particles (Fe^0) with individual particle sizes averaging less than 100 nm, and different synthesis methods may result in different variations (e.g. average nanoparticle size, size distribution, specific surface area). nZVI may also be coated with a variety of surface modifiers for enhanced reactivity or mobility in the environment, including a number of polymers, polyelectrolytes, and surfactants (e.g. He and Zhao 2005; Phenrat et al. 2009a, 2009b; Sirk et al. 2009). These variations may ultimately lead to very different nanoparticle characteristics or surface properties, which may also differ between manufacturers and suppliers.

In the presence of oxygen, the surface of nZVI will quickly oxidize to iron hydroxides or oxyhydroxide (Li et al. 2006). In the sub-surface which typically has oxygen-limited conditions, the surface of nZVI will likely form magnetite (Fe_3O_4) and/or maghemite (Fe_2O_3, γ-Fe_2O_3) depending on oxidation conditions (Reinsch et al. 2010). The formations of these iron oxides will then reduce nZVI's reactivity (Baer et al. 2008; Sarathy et al. 2008). The reactivity of nZVI as well as its mobility in the environment may also be reduced through rapid aggregation and agglomeration processes, in which micro-sized fractal aggregates are often formed (Phenrat et al. 2007; Theron et al. 2008). Aggregation and agglomeration rates are strongly dependent upon both nZVI concentration (Lowry and Casman 2009) as well as on environmental conditions, such as humic acids, ionic strength, and ionic composition (Saleh et al. 2008). Many of the coatings developed for nZVI are intended to reduce aggregation/agglomeration in order to maintain individual particles and thereby control reactivity (e.g. He and Zhao 2005). However, some coatings have also been shown to block available reactor sites on nZVI which are important for reduction mechanisms to occur, thereby reducing its reactivity (Saleh et al. 2008; Kim et al. 2009). Therefore, the applications of various coatings are expected to play large roles in the reactivity and mobility of nZVI and remain an area of current research for optimization.

nZVI applications

Successful injections of nZVI into the sub-surface may be performed through a number of methods, e.g. direct push injections, recirculation through injection/extraction wells, pneumatic fracturing (Quinn et al. 2005; Henn and Waddill 2006). Typical concentrations of nZVI slurries average ~10 g/L (Henn and Waddill 2006; Phenrat et al. 2009b). However, field concentrations as low as 0.75-1.5 g/L (Elliott and Zhang 2001) and as high as 50 g/L (Tuomi et al. 2008) have also been documented. Concentrations used are very site specific and are also dependent on other factors such as source zone architecture, contaminant plume dimensions and type, and environmental conditions.

After nZVI is injected in the sub-surface, its migration will depend not only on properties of nZVI nanoparticles but also to a large extent on factors within the environment (e.g. pH, oxidation reduction potential, groundwater geochemistry and flow, nature of the aquifer materials (Li et al. 2006; Saleh et al. 2008). It has been estimated that the reactive lifespan of nZVI is 4 - 8 weeks depending on the nZVI characteristics as well as surrounding environmental conditions, e.g. pH. However lifespans of 1-2 weeks for small or amorphous particles (He et al. 2007) and up to a year for larger or more crystalline particles have also been observed (Liu and Lowry 2006). Furthermore, laboratory studies have shown that in some instances nZVI may be mobile in the environment for up to 8 months, depending on site hydrogeochemistry and the application of some coatings (Kim et al. 2009), although there is no information from field scale studies regarding this thus far (Grieger et al. 2010a- Paper IV).

Some of the main technical challenges of using nZVI to remediate contaminated soil and groundwater are a successful injection and distribution, including the possibility of porous media clogging around injection points or wells (Henn and Waddill 2006) and/or collision or attachment of nZVI to surfaces in the environment (Lowry and Casman 2009). As briefly mentioned, there are additional challenges in controlling the reactivity of nZVI, due to the formation of iron oxides or aggregation/agglomeration processes, as well as in controlling the mobility of nZVI in the environment. For instance, natural conditions often contain physical or chemical heterogeneities which may also alter the transport of nZVI compared to laboratory column studies, e.g. soil fractures or the presence of humic acids (Grieger et al. 2010a –Paper IV). Due to these challenges along with others, scientists and engineers are currently researching different methods to optimize the use of nZVI for successful environmental remediation, and which is currently an area of active research (e.g. Kim et al. 2008; Saleh et al. 2008; Kim et al. 2009; Phenrat et al. 2009a).

4.2 Environmental risks and uncertainties of nZVI

While the use of nZVI for environmental remediation is proposed as environmentally-beneficial technique with the overall objective of reducing environmental risks from contaminants and improving environmental quality, some have also questioned whether the direct and intentional introduction of these nanoparticles into the environment may also be reason for concern (e.g. (The Royal Society & The Royal Academy of Engineering 2004, 2006; RCEP 2008). This is largely due to the extensive uncertainties regarding the potential environmental risks of nZVI. In fact, The Royal Society and Royal Academy of Engineering recommended that the "use of free…manufactured nanoparticles in environmental applications such as remediation be prohibited until appropriate research has been undertaken and it can be demonstrated that the potential benefits outweigh the potential risks" (The Royal Society & The Royal Academy of Engineering 2006). The US EPA has also targeted nZVI along with six other nanoparticles for closer investigations in the coming years (Morris et al. 2009).

As explained in the previous chapter (Chapter 3), evaluating the environmental risks of NM has been largely based so far on standard approaches to assess the environmental risks of bulk chemicals, including exposure and effect assessments. However to date there have only been a handful of studies which have investigated the toxic and ecotoxic potential of nZVI, and there have been no quantitative estimates of nZVI in the environment largely due to challenges of detecting and quantifying nanoparticles in complex environmental matrices (Hassellov et al. 2008). The following section therefore provides an overview of the main parameters involved in evaluating the potential environmental risks of nZVI based on an in-depth review and analysis by Grieger et al. (2010a- Paper IV). These include factors important in estimating environmental exposures such as the potential for migration, transformation, degradation, persistency, and bioaccumulation, as well as in regards to the ecotoxicity potential of nZVI.

- *Migration in the environment.* Migration of nZVI is expected to be site-dependent and largely influenced by hydrogeological conditions and nZVI properties (Li et al. 2006; Saleh et al. 2008). Migration is important to consider for estimations of nZVI concentrations in the environment, such as the possibility of e.g. 'hot spots' of higher concentrations near injection wells if transport is inhibited as opposed to wider distribution of lower concentrations if transport occurs with relative ease. Migration of uncoated nZVI is estimated to be within a few centimeters in most cases (Tratnyek and Johnson 2006; Saleh et al. 2008), due to aggregation/agglomeration and colliding with surfaces in the environment (Lowry and Casman 2009). However some coatings significantly increased mobility (as intended in some cases, e.g. triblock copolymer-modified nZVI) (Saleh et al. 2008). One estimate suggested that electrosterically-stabilized nZVI could migrate tens to hundreds of meters in unconsolidated sandy aquifer conditions (based on column experiments) (Saleh et al. 2008). Kim et al. (2009) also estimated that coated nZVI may remain mobile in the environment up to 8 months depending on hydrogeochemistry and specific coatings. The role of natural coatings on nZVI mobility as well as long-term environmental behavior and migration are largely unknown.

- *Transformation and degradation in the environment.* As nZVI is highly reactive, transformation processes are expected to occur through chemical (e.g. abiotic, redox transformations) and/or biological processes (e.g. microbial biodegradation). In addition to the oxidation of Fe^0 to iron oxides and the possible coating of natural organic matter (NOM) in the environment, carbonate and sulfide minerals may also precipitate (Reinsch et al. 2010). Degradation of nZVI or its coatings through abiotic or biotic (e.g. microbial) processes is largely unknown, although it has been found that some bacteria may be able to respire on iron oxide nanoparticles (Gerlach et al. 2000). Only one study has investigated the lifetime of some coatings and their ability to desorb, and the authors also raised the possibility that the coatings may serve as carbon sources for bioremediation (Kim et al. 2009).

- *Potential for persistency and bioaccumulation*: Persistency, in terms of the ability to remain the environment (European Union 2006), of 'parent' nZVI nanoparticles and/or any formed 'daughter' particles (e.g. iron oxides) is virtually unknown for nZVI at this time. Due to limited information regarding the ability of nZVI to be degraded or transformed in the environment, no conclusions can be drawn regarding the persistency of nZVI. Similarly, there are currently no data on the uptake of nZVI by organisms or regarding nZVI's bioaccumulation potential.

- *Potential for ecotoxicity*: So far only a very limited number of studies have investigated the toxicity or ecotoxicity potential of nZVI (i.e. <10). In addition, there are a number of other studies which have investigated the (eco)toxicity potential of iron oxide nanoparticles (e.g. Auffan et al. 2006; Karlsson et al. 2009; Zhu et al. 2008) but were not included in this analysis due to the specific focus on nZVI rather than e.g. derivative or transformed nanoparticles. Nonetheless, the data presented in the very limited number of peer-reviewed and published studies suggest that acute toxicity to aquatic organisms is relatively low, although sub-lethal effects have also been observed at lower concentrations (< 1 mg/L, Li et al. 2009). It also appears that nZVI has been documented to be attached to organisms and cells (e.g. Lee et al. 2008) and also cause histopathlogical and morphological changes in some species (Li et al. 2009) and some coatings may decrease toxicity, most likely through reduced adherence (Li et al. 2010). From this limited number of studies, it also appears that adverse effects are thought to be associated with the release of Fe(II) from nZVI, the subsequent production of reactive oxygen species (ROS), and disruptions of cell membranes. Oxidation (aging) of nZVI (Fe^0) under aerobic conditions is also found to reduce toxicity (Li et al. 2010).

4.3 Balancing benefits, risks, and uncertainties

Given the information presented thus far regarding the use of nZVI for *in situ* remediation, how can scientists, engineers, and decision makers more fully consider the potential environmental benefits and risks when deciding upon its use? This is in light of the fact that the standard approach to weighing these aspects (i.e. environmental risk assessment) is unable to be completed for NM.

Weighing these aspects may be especially challenging since they involve considering the mainly known, expected, and immediate benefits to the mainly unknown (and potentially unanticipated) environmental risks, particularly on long-term scales. It should also be stated that in these cases it is not necessarily a choice of 'risk' or 'no risk' because there is already an environmental risk present (i.e. original contaminant). Therefore, the decision may in fact be to choose the 'best available' option to remediate a site which achieves a level of environmental risk 'as low as reasonably achievable' (Vlek 2009) rather than to aim for a complete reduction of environmental risk (Grieger et al. 2010a- Paper IV).

4.3.1 "Best" and "worst" case scenarios

In light of these aspects and the challenges within not only assessing the potential environmental risks of nZVI but also within decision making in these regards, one logical starting point to making risk-based decisions may be a simple exercise of estimating and comparing "best" and "worst" case conditions for an environmental risk to occur (Vlek 2009). Herein, identifying or estimating the "best" and "worst" case conditions forms the ends of a spectrum of possible scenarios in which to frame current conditions based on available data and information. For nZVI, this exercise could be a possible first step to qualitatively consider nZVI's potential environmental risks and related uncertainties. In this case, the criteria used to estimate "best" and "worst" case conditions for nZVI are based on parameters which are commonly used to assess environmental risks of other substances, particularly chemicals, as described in the previous section. These include the potential for: 1) dispersal in the environment (including potential for long-range transport); 2) ecotoxicity (i.e. ability to cause adverse effects to organisms in the environment; 3) persistency (i.e. ability to remain in environment, and for nZVI also the ability to persist in nanoparticulate form); 4) bioaccumulation (i.e. ability to accumulate or concentrate in 'higher order' organisms); 5) reversibility (i.e. ability for removal or to reverse original introduction from environment); 6) possibly mitigate, increase, or not affect the overall level of environmental pollution (Table 4). Using these criteria, the "best'" and "worst" case scenarios for nZVI from an environmental risk perspective are included in Table 4 along with the current state-of-the-art knowledge in these regards.

Based on current knowledge, results show that nZVI's potential to pose an environmental risk is in between "best'" and "worst" case conditions (Table 4). While this main finding is not entirely unexpected, it highlights that at least based on available information there are no significant grounds to conclude that nZVI poses a significant, apparent risk to the environment, although the most serious criteria (i.e. persistency, bioaccumulation, toxicity: PBT) are unknown. Moreover, most data related to the potential risks of nZVI are related to the possible environmental exposures (e.g. dispersal or migration) rather than e.g. long-term ecotoxicological impacts or e.g. reversibility of the technology, especially at field-scale sites.

In regards to whether introducing nZVI into the environment may reduce environmental risks (e.g. degrading contaminants in soil/groundwater), increase environmental risks (e.g. pose a greater risk than original contamination), or not effect the level of environmental risks (e.g. trading new risks of nZVI with older risks from contaminants), these comparisons are likely to be largely context and site dependent. For example, the risks of the original contaminants as well as the sensitivity of the receiving environment are important in framing these discussions of 'how risky' nZVI may be for a given site. A more complete analysis which compares the hazard potentials of the original contaminants with nZVI (or other treatment options) may be needed in such cases.

As the previous exercise has shown that many of the serious, long-term criteria for environmental risks are largely unknown, decision makers may need to actively and transparently include these uncertainties in their decisions regarding nZVI in order to more fully account for them. In addition, decision makers may also need to state their choice or value criteria when considering nZVI as a remediation option, including the handling of unknown, long-term risks. This process of transparently communicating extensive uncertainties within environmental decision making is most likely complex and additional assistance from e.g. environmental agencies may be needed in many cases.

Table 4. "Best" and "worst" case conditions and current state-of-the-art knowledge related to the potential for nZVI to pose an environmental risk, based on commonly used parameters (Grieger et al. 2010 – Paper IV).

Criteria	Scenarios	Current state-of-the-art knowledge
1. Potential for dispersal in environment: Ability to be well-dispersed in the environment, including potential for long-range transport (EU 2006)	**"Best-case":** Does not migrate from injection site (stays within few centimeters)	Uncoated nZVI: limited migration (few centimeters) (Saleh et al. 2008; Tratnyek and Johnson 2006). Coated/stabilized nZVI: enhanced migration, up to tens or hundreds of meters in consolidated sandy aquifers (Saleh et al. 2008). May remain mobile up to 8 months under some hydrogeological conditions with some coatings (Kim et al. 2009). Role of natural coatings unknown, although expected to play an important role in migration.
	"Worst-case": Migrates widely in environment (well-dispersed); Coatings (engineered or natural) enhance dispersal	
2. Potential for ecotoxicity: Ability to cause adverse effects to organisms in the environment (EU 2006)	**"Best-case":** Not toxic to organisms in soil/groundwater matrices; Stimulate bio-degradation of original contaminant(s) and serve as growth media for microbes which may also degrade nZVI	Very limited number of published studies to date. For aquatic organisms, only 1 EC_{50} value for acute toxicity has been published although it is not a peer-reviewed study ($EC_{50,\ 48\ hours}$: 55 mg/L) (Oberdörster et al. 2006). Some studies documented potential for toxicity in some aquatic organisms (fish, daphnia) (Li et al. 2009; Lee et al. 2008) and bacteria (Auffan et al. 2008; Kirschling et al. 2010; Li et al. 2010). Other studies documented toxicity to rodent microglia and neurons (Phenrat et al. 2009b) and human bronchial epithelial cells (Keenan et al. 2009). Effects have been observed as low as 0.5 mg/L (reduction in superoxide dismutase activity in Medaka embryos) (Li et al. 2009). Pronounced effects were seen at 5 mg/L (reduction in superoxide dismutase activity in Medaka embryos and adults, increase of malondialdehyde in embryos, reduced glutathione in adults and histopathological and morphological alterations of gill tissue) (Li et al. 2009). Some applied coatings including NOM may significantly decrease toxicity (Li et al. 2010). Preliminary results suggest slightly to moderately toxic.
	"Worst-case": Toxic to organisms in soil/groundwater, especially microbes responsible for basic ecosystem functions; Toxic to microbes beneficial for site remediation; Toxic to other/higher order organisms later exposed to nZVI through biotransfer or bioaccumulation for instance in surface water or other receptors	
3. Potential for persistency: Ability to remain in the environment (which may be through estimating half-lives); and in the case of nZVI the ability to persist in	**"Best-case":** Not persistent; Easily degraded through abiotic (e.g. chemical/physical) or biotic (e.g. microbial) degradation mechanisms	Generally unknown One study indicates lifetime of some coatings may be on the order of a few years, whereby 30% wt. of polyelectrolyte coating desorbed after 4 months (Kim et al. 2009). Some studies suggest that microbial degradation may be possible through e.g. respiration of iron oxide nanoparticles (Gerlach et al. 2000). The application of coatings will likely affect the potential for degradation, although it is unknown how and to what extent for the wide range of
	"Worst-case": nZVI or transformation products are persistent;	

nanoparticulate form (EU 2006)	Not well-degraded through abiotic or biotic degradation mechanisms	coatings currently developed. Some studies however have documented the lifetime of Fe0 in nZVI (Liu and Lowry2006; Liu et al. 2007).
4. Potential for bioaccumulation: Ability to bioaccumulate or bioconcentrate in 'higher order' organisms (EU 2006)	**"Best-case":** Not bioaccumulative	Unknown
	"Worst-case": Bioaccumulative in species and/or biomagnification in ecosystem	
5. Potential for reversibility: Ability for removal or to reverse original introduction from environment (Collingridge 1980)	**"Best-case":** Easily removed through natural mechanisms (e.g. degradation); Easily extracted through mechanical or technical means	Generally unknown; One study based on laboratory microcosm experiments indicates that the biogeochemistry of aquifer material may start to return to initial states following nZVI oxidation (Kirschling et al. 2010).
	"Worst-case": Removal or reversibility not possible; Difficulty increases particularly if widespread in environment	
6. Potential mitigate, increase, or not effect level of environmental pollution: General ability to alter, by increasing or decreasing, level of environmental pollution	**"Best-case":** Mitigate environmental pollution from successfully degrading original soil/groundwater contaminant(s); Not posing any additional risks to the environment	Generally unknown; Context dependent, including risk of original contaminants, type of nZVI used, and/or sensitivity of ecosystem(s).
	"Worst-case": Maintain or increase level of environmental pollution, possibly: - "Risk-risk" trade-offs (trading original risks with new ones); -Directly or indirectly increase level of environmental pollution, possibly by posing greater risks and/or dispersing original contaminants further through contaminant carrier role	

4.3.2 Other tools and strategies

In addition to estimating "best'" and "worst" case scenarios and comparing the current state of knowledge to these scenarios, there may also be other decision making tools and strategies which may be applied to nZVI. Some of these were previously described in Chapter 3 in regards to alternative frameworks and approaches for NM compared to standard environmental risk assessment. Nonetheless, the only documented and published application of a risk analysis framework or strategy for nZVI thus far has been the application of the Nano Risk Framework by Environmental Defense and Dupont (2007a). However, this framework was unable to be completed due to extensive uncertainties in nZVI risk characterization. In addition, there may also be a number of relatively well-developed tools or strategies which have been used in other environmental risk challenges and which may in theory be applicable to nZVI, such as cost-benefit analysis (Dale et al. 2008), life cycle assessment (Seager and Linkov 2008; Lemming et al. 2010), environmental impact assessment (European Commission 2010), and comparative risk assessment (David 2008). However, many of these tools and strategies are not designed for conditions under extensive uncertainties and therefore their applicability to nZVI is not yet fully clear. This may be similar to cases of other NM.

Moreover, other tools or frameworks which have been proposed for other NM may also be applicable to nZVI, although their fully relevancy for nZVI specifically has not yet been demonstrated. For example, MCDA (Linkov et al. 2007; Tervonen et al. 2009) could potentially be applied to nZVI when deciding upon the use of, for example, different treatment options in which various remediation technologies or different nanoparticles used in treatment options could be ranked relative to specified criteria. This approach may be especially interesting for nZVI, since certain risk attributes such as e.g. potential for persistency or e.g. how heavily to include uncertainty may be transparently shown as a value or choice criteria. In addition, Alternatives Assessment (Martuzzi and Tickner 2004; Rossi et al. 2006; Raphael 2009) may also serve as an interesting decision making tool for nZVI, since e.g. different treatment options may be reviewed and the option with the for instance lowest level of potential environmental risk or uncertainty could be chosen as the best treatment option. In this option, risk evaluators or decision makers may transparently indicate which criteria or values are included in decisions regarding a variety of options. Finally, broader risk governance mechanisms such as the IRGC's Risk

Governance Framework (2007) may also be applicable to nZVI in cases where a wide range of stakeholders may be included in decisions, which may be particularly attractive to regulatory agencies or larger institutes.

4.4 Application of Worst-Case Definition model

Another approach which has been proposed in response to the serious challenges and limitations of environmental risk assessment for NM has been the application of the Worst-Case Definition (WCD) model (Sørensen et al. 2010a) to identify worst-case conditions for risk assessment. In an analysis by Grieger et al. (2010-Paper V in Appendix), estimates of worst-case conditions for environmental risk assessment of nZVI used in environmental remediation were identified. This analysis also applied the WCD model to another nanoparticle (C_{60}) as used in an oil lubricant application as an additive (Bardahl Inc. 2008). However, an overview of this case study is not included in this thesis chapter due to reasons of brevity in demonstrating the use of novel approaches for decision making in regards to the potential risks of selected NM. Applying the WCD model to the case of nZVI aimed to not only identify worst-case conditions for environmental risk assessment but also to help prioritize research efforts for environmental risk assessments in this field.

In general the identification of worst-case conditions has been one approach previously used in environmental and health risk contexts in order to help prioritize or optimize risk assessments (Vlek 2009). Similarly, the WCD model aims to facilitate the identification and evaluation of multi-dimensional, worst-case risk conditions with the main objective of identifying worst-case conditions which are critical to include in worst-case estimates in risk assessments. Thus far, the WCD model has been applied for environmental risk assessment of a pesticide use in Denmark (Sørensen et al. 2010b) as well as to the two nanoparticles (nZVI, C_{60}) by Grieger et al. (2010 – Paper V).

4.4.1 WCD model

The WCD model is essentially a qualitative model that identifies worst-case conditions based on the identification of "Protected Units" (i.e. subjects to protect from a risk, PU) as well as "Causes of Risk" (i.e. causes of a specific risk to occur, CR) (Sørensen et al. 2010a). The PUs are first identified and mapped using knowledge mapping techniques, such as mind maps or division trees. In the case of nZVI, the PUs were the environmental organisms potentially exposed to nZVI through its normal use pattern (i.e. *in situ* injections). In addition, the possibility of spills and leaks at nZVI injection sites were also included in the consideration of potential environmental exposure patterns although exposures through other product life stages (e.g. manufacturing, production, etc.) were excluded. The identified PUs were mapped using mind mapping techniques and then grouped into different types based on life histories of the organisms and habitats in which they live. In total, there were 9 different PUs types identified as critical for inclusion in worst-case conditions for environmental risk of nZVI (Figure 5).

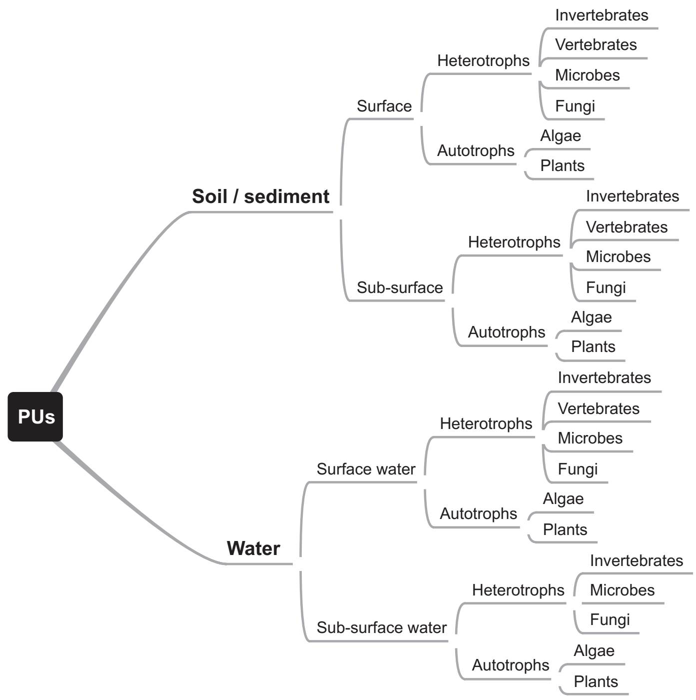


Figure 5. Identified Protected Units (PUs) for the case study involving the *in situ* use of nZVI based on the application of the WCD model (Grieger et al. 2010- Paper V).

Next, the CRs are then identified from the available scientific knowledge and also mapped using knowledge mapping techniques. These are the parameters normally included in traditional exposure and effect assessments (e.g. exposure routes, ecotoxicological effect responses). In the case of nZVI, the identified CRs were those parameters expected to influence an adverse ecotoxicological response following exposure to nZVI. This was based on the available literature regarding potential environmental exposures and ecotoxicology of nZVI (see previous sections on environmental risks of nZVI). In cases of data or knowledge gaps, knowledge pertaining to the potential environmental risks of other nanoparticles or within the field of ecotoxicology or environmental risk assessment was also used. The CRs were then numbered according to their hierarchical division to facilitate their handling and use. The most 'specific' CRs (i.e. parameters which have not been further divided into any additional underlying causes) are then used in subsequent steps of the analysis. In total, there were 40 separate CRs identified in this analysis (Figure 6).

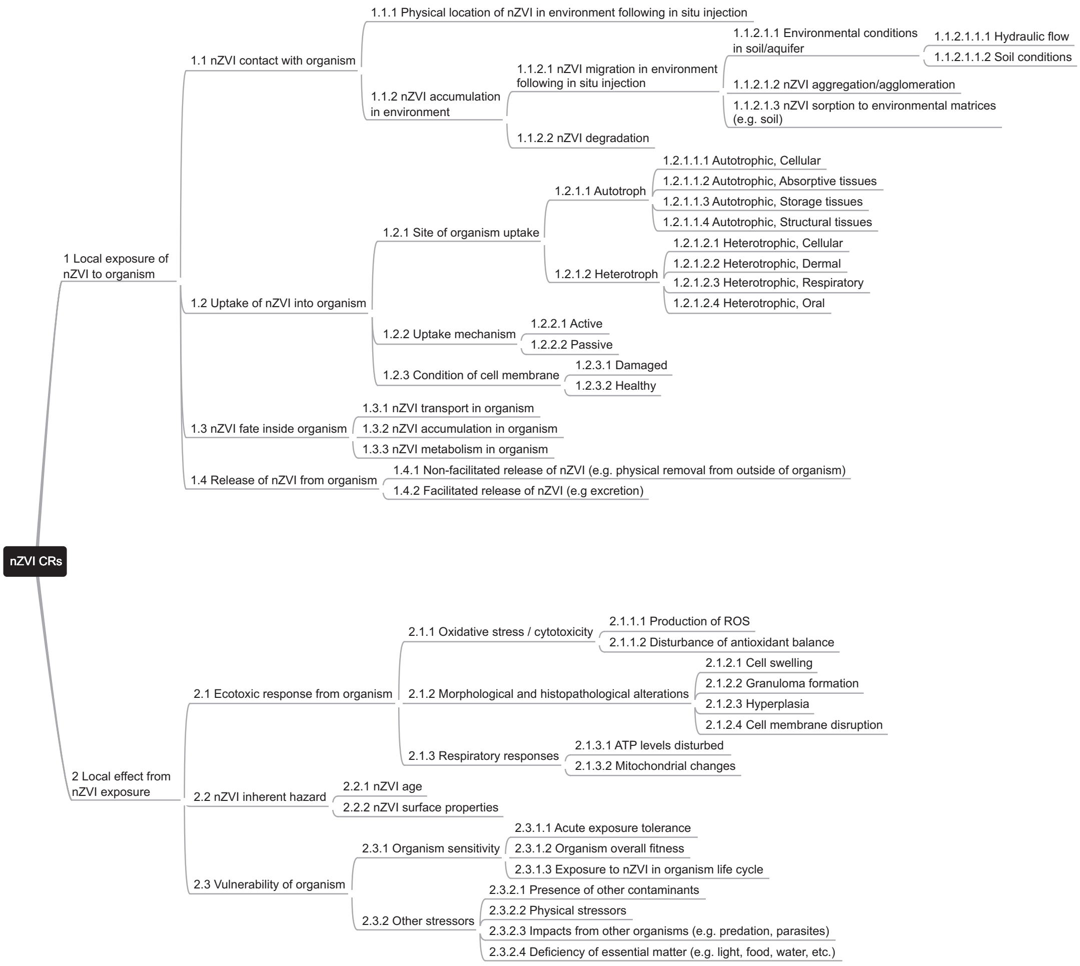


Figure 6. Identified Causes of Risk (CRs) for the case study involving the *in situ* use of nZVI based on the application of the WCD model (Grieger et al. 2010- Paper V).

It should be clearly stated that the level of detail to include in identifying PUs and CRs according to the WCD model is very critical. Sørensen et al. (2010a) recommends that a "useful" level of detail is ideal. It is recognized that this is indeed a very subjective process of determining a "useful" level of detail, and different e.g. stakeholders and risk assessors may define this level of detail differently. Moreover, when identifying and mapping the CRs there will likely be some overlap between different underlying causes of an identified risk. In this, a balance should therefore be maintained between providing "too little" and "too much" detail in order to facilitate usefulness and consistency in describing different CR cause-effect relationships.

The next step in the WCD model is to then rank the PUs according to how "important" they are for protection (e.g. some organisms may be more "valuable" than others) using a 3-point system (1=low importance, 2=medium importance, and 3=high importance). A PU should be considered particularly important if it is "valuable" to the risk problem in question, e.g. umbrella or keystone species or important for ecosystem functioning. In the case of nZVI, the importance ranking of PUs was made using the following criteria: '1' was assigned to organisms which serve limited or at least some ecosystem functions but were i) lower in their overall relative importance for the ecosystem or ii) were not expected to be a major component of the ecosystem; '2' to organisms which serve i) some major ecosystem function, ii) were higher level organisms, and/or iii) were food sources for other organisms but may not be very populous in the ecosystem or the majority of the organism's body/entity is not likely to be exposed to nZVI; '3' to organisms which were i) higher level organisms, ii) serve major ecosystem functions, iii) form a basis for the food chain, iv) and/or may potentially be a source of bioaccumulation (Table 5).

In addition, the CRs were also ranked according to how "important" they are to cause an increase in the risk level of each PU (i.e. PU-CR relationships). A PU-CR relationship is deemed "important" if it significantly increases the risk for a relevant PU, and should be made independent of different PU types. In the case of nZVI, PU-CR relationships were ranked according to the available ecotoxicological knowledge of nZVI in which a value of '1' was given to PU-CR relationships which were considered to pose a possible environmental risk, '2' to PU-CR relationships which may moderately increase the possibility of risk, and '3' to PU-CR relationships which may significantly increase the possibility of risk (Table 6). Ultimately, the combinations of the most "important" PUs and the most "important" PU-CR relationships (i.e. '3-3' combinations) are the most probable worst-case conditions which are critical for inclusion in subsequent risk assessments. It should be clearly stated that this method does not find the absolute, de facto worst-case conditions but rather uses existing knowledge in a structured manner to identify most probable estimates for worst-case conditions.

4.4.2 Estimates for worst-case conditions

Based on the ranking criteria for PUs and PU-CR relationships previously described, estimates for worst-case conditions for environmental risk assessment for nZVI are shown in the shaded cells of Table 6. In total there were 56 separate worst-case conditions identified, comprised of 16 different CRs.

For vertebrates inhabiting surface soil/sediment and water matrices, estimated parameters for worst-case conditions include dermal exposure route for site of uptake (1.2.1.2.2), exposure of nZVI in organism life cycle (2.3.1.3), and nZVI metabolism in organism (1.3.3). For microbes in surface and sub-surface soils/sediments and surface water matrices, estimates for worst-case conditions include active nZVI uptake by cells (1.2.2.1), nZVI accumulation in organism (1.3.2), different mechanisms of ecotoxicity (ROS production, antioxidant balance disturbance, cell membrane disruption) (2.1.1.1-2.1.2.4), nZVI age (2.2.1) and surface properties (2.2.2), and acute exposure tolerance (2.3.1.1).

Table 5. Identified PUs and their relative importance rankings based on the application of the WCD model (Grieger et al. 2010- Paper V).

H = Heterotroph; A = Autotroph; Invert = Invertebrates; Vert. = Vertebrates; Micro = Microbes

PUs and ranking					Argument for relative importance
Soil / sediment	Surface	H	Invert.	2	Serve some ecosystem functions and are food sources for other organisms
			Vert.	3	Higher level ecosystem organisms; potential for bioaccumulation
			Micro.	3	Serve major ecosystem functions (e.g. degradation, nutrient cycling, etc.)
			Fungi	1	Serve some ecosystem functions (e.g. degradation) but lower overall relative importance
		A	Algae	2	Serve some (major) ecosystem functions but not expected to be very populous
			Plants	3	Serve major ecosystem functions and basis for food chain
	Sub-surface	H	Invert.	2	Serve some ecosystem functions and are food sources for other organisms
			Vert.	2	Higher level ecosystem organisms but not expected to be very populous
			Micro.	3	Serve major ecosystem functions (e.g. degradation, nutrient cycling, etc.)
			Fungi	1	Not expected to serve many ecosystem functions and not likely to be very populous
		A	Algae	2	Serve some ecosystem functions and are food sources for other organisms
			Plants	2	Serve some ecosystem functions but majority of organism is not exposed; only roots or other subsurface structures
Water	Surface	H	Invert.	2	Serve some ecosystem functions and are food sources for other organisms
			Vert.	3	Higher level ecosystem organisms; potential for bioaccumulation
			Micro.	3	Serve major ecosystem functions (e.g. degradation, nutrient cycling, etc.)
			Fungi	1	Serve some ecosystem functions (e.g. degradation) but lower overall relative importance
		A	Algae	3	Serve some ecosystem functions and basis for food chain
			Plants	3	Serve some ecosystem functions and basis for food chain
	Sub-surface	H	Invert.	1	Not expected to serve many ecosystem functions and not likely to be very populous
			Micro.	3	Serve major ecosystem functions (e.g. degradation, nutrient cycling, etc.)
			Fungi	1	Not expected to serve many ecosystem functions and not likely to be very populous
		A	Algae	1	Not expected to serve many ecosystem functions and not likely to be very populous
			Plants	2	Majority of organism is not exposed; only roots or other subsurface structures

Table 6. Relative importance rankings of PUs and PU-CR relationships for nZVI, and identification of worst-case conditions (shaded cells) (Grieger et al. 2010-Paper V).

H = Heterotroph; A = Autotroph; Invert = Invertebrates; Vert. = Vertebrates; Micro = Microbes

			PU	PU rank	1.1.1 Physical location of nZVI in environment	1.1.2.1.1.1 Hydraulic flow	1.1.2.1.1.2 Soil conditions	1.1.2.1.2 nZVI aggregation/agglomeration	1.1.2.1.3 nZVI sorption to environmental matric	1.1.2.2 nZVI degradation	1.2.1.1.1 Autotrophic, Cellular	1.2.1.1.2 Autotrophic, Absorptive tissues	1.2.1.1.3 Autotrophic, Storage tissues	1.2.1.1.4 Autotrophic, Structural tissues	1.2.1.2.1Heterotrophic, Cellular	1.2.1.2.2 Heterotrophic, Dermal	1.2.1.2.3 Heterotrophic, Respiratory	1.2.1.2.4 Heterotrophic, Oral	1.2.2.1 Active	1.2.2.2 Passive	1.2.3.1 Damaged	1.2.3.2 Healthy	1.3.1 nZVI transport in organism	1.3.2 nZVI accumulation in organism	1.3.3 nZVI metabolism in organism	1.4.1 Non-facilitated release of nZVI	1.4.2 Facilitated release of nZVI (e.g. excretion)	2.1.1.1 Production of ROS	2.1.1.2 Disturbance of antioxidant balance	2.1.2.1 Cell swelling	2.1.2.2 Granuloma formation	2.1.2.3 Hyperplasia	2.1.2.4 Cell membrane disruption	2.1.3.1 ATP levels disturbed	2.1.3.2 Mitochondrial changes	2.2.1 nZVI age	2.2.2 nZVI surface properties	2.3.1.1 Acute exposure tolerance	2.3.1.2 Organism overall fitness	2.3.1.3 Exposure to nZVI in organism life cycle	2.3.2.1 Presence of other contaminants	2.3.2.2 Physical stressors	2.3.2.3 Impacts from other organisms	2.3.2.4 Deficiency of essential matter
Soil/sediment	Surface	H	Invert.	2	2	0	1	1	1	2	0	0	0	0	1	1	0	2	2	1	2	1	2	3	1	2	2	2	2	2	0	0	2	0	0	1	2	3	0	2	1	1	1	1
			Vert.	3	2	0	1	1	1	1	0	0	0	0	1	**3**	2	2	1	1	0	0	2	2	**3**	1	1	2	2	2	1	1	2	1	1	1	1	2	2	**3**	0	1	1	1
			Micro.	3	2	0	2	2	2	2	0	0	0	0	2	0	0	0	**3**	1	2	1	0	**3**	2	2	2	**3**	**3**	0	0	0	**3**	1	1	**3**	**3**	**3**	0	1	1	1	1	1
			Fungi	1	2	0	1	2	2	2	0	0	0	0	1	0	0	0	1	1	1	0	1	2	1	1	1	3	3	1	0	0	3	0	0	2	1	2	0	1	0	1	1	1
		A	Algae	2	2	0	1	2	2	2	3	2	0	0	0	0	0	0	2	1	2	1	0	3	1	2	2	3	2	0	0	0	3	1	1	3	3	3	0	1	1	1	1	1
			Plants	3	2	0	2	1	1	1	2	2	2	1	0	0	0	0	2	1	**3**	1	2	2	2	1	1	2	2	0	0	0	**3**	0	0	2	2	2	2	1	1	1	1	1
	Sub-surface	H	Invert.	2	3	2	2	2	1	2	0	0	0	0	2	2	0	2	2	1	2	1	3	3	1	2	2	2	2	2	0	0	2	0	0	2	2	2	0	2	2	1	1	1
			Vert.	2	2	1	2	2	1	1	0	0	0	0	1	3	1	3	1	1	0	0	2	2	3	1	1	2	2	2	1	1	2	1	1	2	2	2	2	3	1	1	1	1
			Micro.	3	2	2	2	2	2	2	0	0	0	0	2	0	0	0	**3**	1	2	1	0	**3**	2	2	2	**3**	**3**	0	0	0	**3**	1	1	**3**	**3**	**3**	0	1	2	1	1	1
			Fungi	1	2	1	1	2	2	2	0	0	0	0	1	0	0	0	1	1	1	0	1	2	1	1	1	3	3	1	0	0	3	0	0	2	1	2	0	1	1	1	1	1
		A	Algae	2	2	1	2	2	2	2	3	1	0	0	0	0	0	0	2	1	2	1	0	3	1	2	2	3	2	0	0	0	3	1	1	3	3	2	0	1	2	1	1	1
			Plants	2	2	2	2	1	1	1	2	2	2	1	0	0	0	0	2	1	3	1	2	2	2	1	1	2	2	0	0	0	2	0	0	1	2	2	2	1	2	1	1	1
Water	Surface water	H	Invert.	2	2	1	0	1	1	2	0	0	0	0	1	1	0	2	2	1	2	1	2	3	1	2	2	2	2	2	0	0	2	0	0	1	2	3	0	2	1	1	1	1
			Vert.	3	2	1	0	1	1	1	0	0	0	0	1	**3**	2	2	1	1	0	0	2	2	**3**	1	1	2	2	2	1	1	2	1	1	1	1	2	2	**3**	0	1	1	1
			Micro.	3	2	1	0	2	2	2	0	0	0	0	2	0	0	0	**3**	1	2	1	0	**3**	2	2	2	**3**	**3**	0	0	0	**3**	0	0	**3**	**3**	**3**	0	1	1	1	1	1
			Fungi	1	2	1	0	2	2	2	0	0	0	0	1	0	0	0	1	1	1	0	1	2	1	1	1	3	3	1	0	0	3	0	0	2	1	2	0	1	0	1	1	1
		A	Algae	3	**3**	1	0	2	1	2	**3**	1	0	0	0	0	0	0	2	1	2	1	0	**3**	1	2	2	**3**	**3**	0	0	0	**3**	1	1	**3**	**3**	**3**	0	1	1	1	1	1
			Plants	3	**3**	1	0	1	1	1	2	2	2	1	0	0	0	0	2	1	**3**	1	2	2	2	1	1	2	2	0	0	0	**3**	0	0	2	2	2	2	1	1	1	1	1
	Sub-surface water	H	Invert.	1	3	3	3	2	1	2	0	0	0	0	2	2	0	2	2	1	2	1	3	3	1	2	2	2	2	2	0	0	2	0	0	2	2	2	0	2	2	1	1	1
			Micro.	3	**3**	**3**	**3**	2	2	2	0	0	0	0	2	0	0	0	**3**	2	**3**	1	0	**3**	2	2	2	**3**	**3**	0	0	0	**3**	0	0	**3**	**3**	**3**	0	1	2	1	1	1
			Fungi	1	2	2	2	2	2	2	0	0	0	0	1	0	0	0	1	1	1	0	1	2	1	1	1	3	3	1	0	0	3	0	0	2	1	2	0	1	1	1	1	1
		A	Algae	1	2	3	3	2	2	2	3	1	0	0	0	0	0	0	2	1	2	1	0	3	1	2	2	3	3	0	0	0	3	1	1	3	3	2	0	1	2	1	1	1
			Plants	2	3	3	3	1	1	1	2	2	2	0	0	0	0	0	2	1	3	1	2	2	2	1	1	2	2	0	0	0	2	0	0	1	2	2	2	1	2	1	1	1

For microbes inhabiting sub-surface water matrices, estimates for worst-case conditions also include the physical location of nZVI in the environment (1.1.1), hydraulic flow (1.1.2.1.1.1), soil conditions (1.1.2.1.1.2), as well as damaged cell membrane conditions (1.2.3.1). For algae inhabiting surface waters, estimated worst-case conditions include physical location of nZVI in environment (1.1.1), autotrophic cellular exposure routes (1.2.1.1.1), accumulation in organism (1.3.2), some ecotoxic responses (i.e. production of ROS (2.1.1.1), disturbance of antioxidant balance (2.1.1.2), and membrane disruption (2.1.2.4)), nZVI surface properties (2.2.2), acute exposure tolerance (2.3.1.1), and nZVI age (2.2.1). Finally, for plants inhabiting surface soil/sediment and water matrices estimates for worst-case conditions include damaged cell membrane (1.2.3.1), the ecotoxic effect of cell membrane disruption (2.1.2.4), and physical location of nZVI in the environment in surface waters (1.1.1).

These identified estimates for worst-case conditions are those parameters which are critical for inclusion in subsequent environmental risk assessments of nZVI in *in situ* applications, and which may also be used to help maximize the efficiencies of risk assessments in this field.

4.5 Study limitations

It is recognized that the applications of “best” and “worst” case scenarios (Grieger et al. 2010a- Paper IV) and the WCD model to identify most probable estimates for worst-case conditions for nZVI (Grieger et al. 2010- Paper V) may have a number of limitations. For instance, they are both based on currently-available data pertaining to nZVI and its potential environmental risks, which at this time are extremely limited (similar to the case of other NM). Therefore, results from these analyses may be contingent upon the currently-available information in these regards. Furthermore, the application of the WCD model was found to be rather lengthy and labor-intensive, and therefore its applicability to other NM may be limited to specific cases of NM use, similar to its application of nZVI. Finally, these applications of novel methods to environmental risk contexts of nZVI are among the first applications of alternative methods to standard environmental risk assessment for NM, and it is likely that more time may be needed to strength these methods not only for nZVI but for their applicability for other NM.

4.6 Main findings for environmental risks and decision making for nZVI

- nZVI may indeed be a promising *in situ* remediation option for some contaminated sites, mainly due to its cost-effectiveness and effectiveness compared to other *in situ* options. However, it also appears that these expected benefits are mainly based on near-term assessments and extensive uncertainties which are especially on long-term timescales may not be fully factored into these assessments due to a lack of data
- Due to many challenges of completing standard environmental risk assessment frameworks for nZVI, other risk analysis or decision support tools may be needed in order to comprehensively weigh the expected environmental benefits, risks, and extensive uncertainties of nZVI
- Grieger et al. (2010-Paper IV) apply a "best" and "worst" case scenario evaluation in order to qualitatively evaluate the current knowledge regarding the potential environmental risks of nZVI
- Based on the current state of knowledge, nZVI's potential to pose as an environmental risk was found to be in between "best" and "worst" case conditions, indicating that thus far there do not appear to be significant grounds to form the basis that nZVI poses an extreme, apparent risk to the environment. However, it should be clearly stated that most of the most serious criteria for environmental consider (i.e. PBT) are largely unknown
- Grieger et al. (2010-Paper V) also applied the WCD model to identify estimates for worst-case conditions which are critical to include in subsequent environmental risk assessments of nZVI
- It was found that there were 56 separate most probable estimates for worst-case conditions, comprised of 16 different CRs. The most frequently included CRs in these worst-case conditions included: nZVI accumulation in organism (1.3.2), production of ROS (2.1.1.1), disturbance of antioxidant balance (2.1.1.2), cell membrane disruption (2.1.2.4), nZVI age (2.2.1), nZVI surface properties (2.2.2), acute exposure tolerance (2.3.1.1)
- These analyses demonstrate the use of novel methods which may be applied in environmental risk contexts of nZVI and potentially for other NM given the extensive challenges within applying standard environmental risk assessment for NM

5 Conclusions and recommendations

Based on the results presented in the preceding chapters, a number of key conclusions are drawn. First, there are extensive knowledge gaps in nearly all aspects of basic EHS knowledge of NM risks, although further research efforts are likely to reduce most uncertainties due to their mainly epistemic nature. In addition, the estimated level of uncertainty indicates that possible outcomes from NM exposure are starting to be understood but probabilities related to these are largely unknown. Second, despite the fact that completing standard risk assessment for NM is expected to be very time- and resource- consuming, NM risk research has primarily been directed at ultimately fulfilling this assessment paradigm. At the same time, a number of alternative risk analysis frameworks have been recently proposed for NM and many of them include a number of important criteria for successful NM risk analysis. However most frameworks are mainly applicable to health (occupational) settings with minimal environmental risk considerations and there were very limited numbers of concrete applications to NM or nano-applications. Third, using novel approaches for decision making regarding the potential environmental risks of nanoparticles used for environmentally-beneficial applications, it was found that nZVI's potential to pose an environmental risk is in between "best" and "worst" case conditions based on currently available data. An additional application of novel approaches for decision making for nZVI also identified the most probable worst-case conditions which are critical for inclusion in environmental risk assessments of nZVI.

These main findings indicate that the field of nano(eco)toxicology is indeed in a very early stage, both in terms of understanding the behavior of NM in environmental systems as well as formulating the best strategies to assess their potential environmental and health impacts. It is likely that knowledge in these fields will progress accordingly, although dedicated research efforts (and time needed to complete them) are clearly needed. While it is understandable that research which aims to assess the potential environmental and health risks of NM proceeds alongside research which also aims to develop adequate assessment tools and frameworks, it also appears to be quite challenging to concurrently test 'new materials' with 'new tools.' Given the speed of science and innovation, it is likely that the main issues presented in this thesis may also be applicable to other emerging environmental risks.

In addition to these conclusions, a number of recommendations are made for research priorities and strategies to better understand and assess the environmental risks of NM. First, it is recommended that research should be prioritized towards the development of adequate assessment testing procedures and equipment as well as full characterization of NM. This is due to the potential for research to effectively reduce uncertainties in the short term given the minimal presence of stochastic uncertainty in these areas. Research should also be prioritized towards better understanding the environmental fate and behavior of various NM as it was one of the most frequently cited areas of uncertainty. It is also recommended that increased attention should be given to issues of bioaccumulation and persistency of NM given previous experiences with POPs and some antimicrobial traits of some NM (e.g. nano-Ag) which may be problematic for environmental or microbial degradation. Thus far, research in these fields has only been scarcely studied so far with only a handful of analyses focusing on the bioaccumulation, persistency, or degradability of NM.

In regards to frameworks and strategies to assess the environmental risks of NM, it is recommended that care should be taken when selecting the most appropriate risk analysis strategy(ies) for a given NM environmental risk context. This is due to the differences in scope and objectives of the various frameworks which have been proposed for NM, and it is therefore expected that not all risk analysis frameworks may be equally applicable or appropriate for a given environmental risk context. In light of this, a multi-faceted approach may be one option to assess the environmental risks of NM in a given context, in which different frameworks (or parts thereof) may be combined to maximize the overall utility or strengths for NM. It is also recommended that the proposed frameworks for NM are more thoroughly tested on a variety of NM with a specific focus on environmental risk considerations. This could be performed using NM which are known to enter environmental matrices such as nanoparticles used for environmental remediation (e.g. nZVI) or those expected in wastewater treatment plants (e.g. nano-Ag). In addition, the investigated frameworks should incorporate more comprehensive strategies to include uncertainty in their current formats, such as the use of e.g. descriptive information (e.g. Walker and Harremoës framework) or more complex methods (e.g. NUSAP, sensitivity analysis). Furthermore, it is recommended that the proposed frameworks develop easily accessible and user-friendly formats (or guides), preferably within compiled documents, which clearly and transparently show both theoretical steps and processes for completion as well as documented case studies using real-world NM or nano-applications applicable for environmental risk contexts. This would significantly aid the further testing and development of the proposed alternative frameworks, and may potentially support their serious consideration as alternative or complimentary to standard (environmental) risk assessment strategies.

In order to promote the sustainable use of nanoparticles in environmentally-beneficial applications such as the *in situ* use of nZVI, it is recommended that research should be specifically dedicated to better understand their ecotoxicological effects, including response mechanisms, uptake ability by a variety of organisms, as well as their full characterization in these assessments. Continued research should also be dedicated to promote their sustainable use, such as through developing coatings which may decrease toxicity or through short- and long-term monitoring of sites which actively use nanoparticles for remediation, particularly focusing on issues of long-term ecotoxicological effects and persistency. Finally, it is recommended that there is better communication and information exchange between NM developers and scientists working in the fields of nano-risks in order to minimize research redundancies as much as possible. This type of information exchange is expected to best occur through funded research projects and platforms dedicated to the responsible innovation of NM, especially for projects aimed towards developing environmentally-sustainable nanotechnologies or NM.

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Appendix

I. Grieger K, Hansen SF, Baun A. 2009. The known unknowns of nanomaterials: Describing and characterizing uncertainty within environmental, health and safety risks. Nanotoxicology 3(3):1-12.

II. Grieger K, Baun A, Owen, R. 2010. Redefining risk research priorities for nanomaterials. Journal of Nanoparticle Research 2(2):383–392.

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V. Grieger K, Hansen SF, Sørensen PB, Baun A. 2010. Conceptual modeling for identification of worst case conditions in environmental risk assessment of nanomaterials using nZVI and C_{60} as case studies. Science of the Total Environment– *Submitted*

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